



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 309/28, A61K 31/55	A1	(11) International Publication Number: WO 96/26933 (43) International Publication Date: 6 September 1996 (06.09.96)								
<p>(21) International Application Number: PCT/US96/02882</p> <p>(22) International Filing Date: 26 February 1996 (26.02.96)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>08/395,245</td> <td>27 February 1995 (27.02.95)</td> <td>US</td> </tr> <tr> <td>08/476,946</td> <td>6 June 1995 (06.06.95)</td> <td>US</td> </tr> <tr> <td>08/580,567</td> <td>29 December 1995 (29.12.95)</td> <td>US</td> </tr> </table> <p>(60) Parent Application or Grant (63) Related by Continuation US Not furnished (CIP) Filed on Not furnished</p> <p>(71) Applicant (for all designated States except US): GILEAD SCIENCES INC. [US/US]; 353 Lakeside Drive, Foster City, CA 94404 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BISCHOFBERGER, Norbert; W. [AT/US]; 105 Glasgow Lane, San Carlos, CA 94070 (US). KIM, Choung, U. [US/US]; 1750 Elizabeth Street, San Carlos, CA 94070 (US). LEW, Willard [US/US]; 717 Guildford Avenue, San Mateo, CA 94402 (US). LIU, Hongtao [CN/US]; 1354 Marlin Avenue, Foster City, CA</p>	08/395,245	27 February 1995 (27.02.95)	US	08/476,946	6 June 1995 (06.06.95)	US	08/580,567	29 December 1995 (29.12.95)	US	<p>94404 (US). WILLIAMS, Matthew, A. [US/US]; Apartment C, 1077 Foster City Boulevard, Foster City, CA 94404 (US).</p> <p>(74) Agents: BOSSE, Mark, L. et al.; Gilead Sciences, Inc., 353 Lakeside Drive, Foster City, CA 94404 (US).</p> <p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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08/580,567	29 December 1995 (29.12.95)	US								
<p>(54) Title: NOVEL SELECTIVE INHIBITORS OF VIRAL OR BACTERIAL NEURAMINIDASES</p> <p>(57) Abstract</p> <p>Novel compounds are described. The compounds generally comprise an acidic group, a basic group, a substituted amino or N-acyl and a group having an optionally hydroxylated alkane moiety. Pharmaceutical compositions comprising the inhibitors of the invention are also described. Methods of inhibiting neuraminidase in samples suspected of containing neuraminidase are also described. Antigenic materials, polymers, antibodies, conjugates of the compounds of the invention with labels, and assay methods for detecting neuraminidase activity are also described.</p>										

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NOVEL SELECTIVE INHIBITORS OF VIRAL OR BACTERIAL NEURAMINIDASES

10

Background of the InventionField of the Invention

15 Neuraminidase (also known as sialidase, acylneuraminyl hydrolase, and EC 3.2.1.18) is an enzyme common among animals and a number of microorganisms. It is a glycohydrolase that cleaves terminal alpha-ketosidically linked sialic acids from glycoproteins, glycolipids and oligosaccharides. Many of the microorganisms containing neuraminidase are pathogenic to man and other animals including fowl, horses, swine and seals. These pathogenic organisms include influenza virus.

20 Neuraminidase has been implicated in the pathogenicity of influenza viruses. It is thought to help the elution of newly synthesized virions from infected cells and assist in the movement of the virus (through its hydrolase activity) through the mucus of the respiratory tract.

25

Brief Description of Related Art

Itzstein, M. von et al.; "Nature", 363(6428):418-423 (1993), discloses the rational design of sialidase-based inhibitors of influenza virus replication.

30 Colman, P. M. et al.; International Patent Publication No. WO 92/06691 (Int. App. No. PCT/AU90/00501, publication date April 30, 1992), Itzstein, L. M. von et al.; European Patent Publication No. 0 539 204 A1 (EP App. No. 92309684.6, publication date April 28, 1993), and Itzstein, L. M. von et al.; International Publication No. WO 91/16320 (Int. App. No. PCT/AU91/00161, publication date October 31, 1991) disclose compounds that bind
35 neuraminidase and are asserted to exhibited antiviral activity *in vivo*.

Objects of the Invention

A principal object of the invention is inhibition of viruses, in particular influenza viruses. In particular, an object is inhibition of glycolytic enzymes such as neuraminidase, in particular the selective inhibition of viral or bacterial neuraminidases.

An additional object of the invention is to provide neuraminidase inhibitors that have a retarded rate of urinary excretion, that enter into nasal or pulmonary secretions from the systemic circulation, that have sufficient oral bioavailability to be therapeutically effective, that possess elevated potency, that exhibit clinically acceptable toxicity profiles and have other desirable pharmacologic properties.

Another object is to provide improved and less costly methods for synthesis of neuraminidase inhibitors.

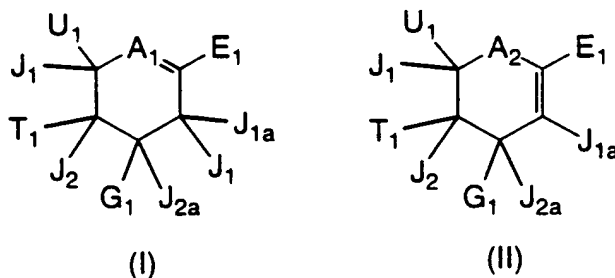
A still further object is to provide improved methods for administration of known and novel neuraminidase inhibitors.

An additional object is to provide compositions useful in preparing polymers, surfactants or immunogens and for use in other industrial processes and articles

These and other objects will be readily apparent to the ordinary artisan from consideration of the invention as a whole.

Summary of the Invention

Compounds, or compositions having formula (I) or (II) are provided herein:



wherein

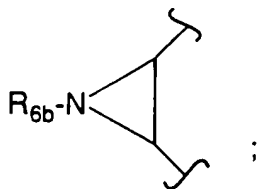
A₁ is -C(J₁)=, or -N=;

A₂ is -C(J₁)₂-, -N(J₁)-, -N(O)(J₁)-, -N(O)=, -S-, -S(O)-, -S(O)₂- or -O-;

E₁ is -(CR₁R₁)_{m1}W₁;

G₁ is N₃, -CN, -OH, -OR_{6a}, -NO₂, or -(CR₁R₁)_{m1}W₂;

T₁ is -NR₁W₃, a heterocycle, or is taken together with U₁ or G₁ to form a group having the structure



U₁ is H or -X₁W₆;

5 J₁ and J_{1a} are independently R₁, Br, Cl, F, I, CN, NO₂ or N₃;

J₂ and J_{2a} are independently H or R₁;

R₁ is independently H or alkyl of 1 to 12 carbon atoms;

R₂ is independently R₃ or R₄ wherein each R₄ is independently substituted with 0 to 3 R₃ groups;

10 R₃ is independently F, Cl, Br, I, -CN, N₃, -NO₂, -OR_{6a}, -OR₁, -N(R₁)₂, -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, -SR_{6a}, -S(O)R₁, -S(O)₂R₁, -S(O)OR₁, -S(O)OR_{6a}, -S(O)₂OR₁, -S(O)₂OR_{6a}, -C(O)OR₁, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R₁, -N(R₁)(C(O)R₁), -N(R_{6b})(C(O)R₁), -N(R₁)(C(O)OR₁), -N(R_{6b})(C(O)OR₁), -C(O)N(R₁)₂, -C(O)N(R_{6b})(R₁), -C(O)N(R_{6b})₂, -C(NR₁)(N(R₁)₂),
15 -C(N(R_{6b}))(N(R₁)₂), -C(N(R₁))(N(R₁)(R_{6b})), -C(N(R_{6b}))(N(R₁)(R_{6b})), -C(N(R₁))(N(R_{6b})₂), -C(N(R_{6b}))(N(R_{6b})₂), -N(R₁)C(N(R₁))(N(R₁)₂), -N(R₁)C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)₂), -N(R_{6b})C(N(R₁))(N(R₁)₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)₂), -N(R_{6b})C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)(R_{6b})),
20 -N(R₁)C(N(R₁))(N(R_{6b})₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)(R_{6b})), -N(R_{6b})C(N(R₁))(N(R_{6b})₂), -N(R₁)C(N(R_{6b}))(N(R_{6b})₂), -N(R_{6b})C(N(R_{6b}))(N(R_{6b})₂), =O, =S, =N(R₁) or =N(R_{6b});

R₄ is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

25 R₅ is independently R₄ wherein each R₄ is substituted with 0 to 3 R₃ groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R₃ groups;

30 R_{6a} is independently H or an ether- or ester-forming group;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

5 W_2 is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W_3 is W_4 or W_5 ;

W_4 is R_5 or $-C(O)R_5$, $-C(O)W_5$, $-SO_2R_5$, or $-SO_2W_5$;

10 W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

W_6 is $-R_5$, $-W_5$, $-R_{5a}W_5$, $-C(O)OR_{6a}$, $-C(O)R_{6c}$, $-C(O)N(R_{6b})_2$, $-C(NR_{6b})(N(R_{6b})_2)$, $-C(NR_{6b})(N(H)(R_{6b}))$, $-C(N(H)(N(R_{6b})_2))$, $-C(S)N(R_{6b})_2$, or $-C(O)R_2$;

15 X_1 is a bond, $-O-$, $-N(H)-$, $-N(W_6)-$, $-N(OH)-$, $-N(OW_6)-$, $-N(NH_2)-$, $-N(N(H)(W_6))-$, $-N(N(W_6)_2)-$, $-N(H)N(W_6)-$, $-S-$, $-SO-$, or $-SO_2-$; and

each m_1 is independently an integer from 0 to 2;

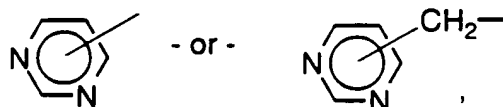
provided, however, that compounds are excluded wherein:

(a) A_1 is $-CH=$ or $-N=$ and A_2 is $-CH_2-$;

(b) E_1 is $COOH$, $P(O)(OH)_2$, $SOOH$, SO_3H , or tetrazol;

20 (c) G_1 is CN , $N(H)R_{20}$, N_3 , SR_{20} , OR_{20} , guanidino, $-N(H)CN$

$$\begin{array}{c} N-R_{20} \quad NR_{20} \quad N \rightarrow O \quad -NHN-R_{20} \\ | \quad \quad | \quad \quad | \quad \quad | \\ OR_{20} \quad R_{20} \quad R_{20} \quad R_{20}R_{20} \end{array}$$



(d) T_1 is $-NHR_{20}$;

(e) R_{20} is H; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; an allyl group or an unsubstituted aryl group or an aryl substituted by a halogen, an OH group, an NO_2 group, an NH_2 group or a $COOH$ group;

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(f) J_1 is H and J_{1a} is H, F Cl, Br or CN;

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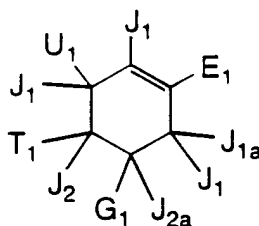
(g) J_2 is H and J_{2a} is H, CN or N_3 ;

(h) U_1 is CH_2YR_{20a} , $CHYR_{20a}CH_2YR_{20a}$ or $CHYR_{20a}CHYR_{20a}CH_2YR_{20a}$;

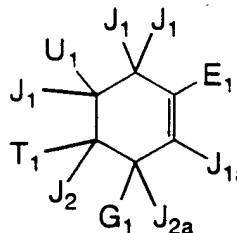
- (i) R_{20a} is H or acyl having 1 to 4 carbon atoms;
 (j) Y is O, S, H or NH;
 (k) 0 to 2 YR_{20a} are H, and
 (l) successive Y moieties in a U₁ group are the same or
 5 different, and when Y is H then R_{20a} is a covalent bond,
 and *provided* that if G₁ is N₃ then U₁ is not -CH₂OCH₂Ph.
 and the pharmaceutically acceptable salts and solvates
 thereof;

and the salts, solvates, resolved enantiomers and purified diastereomers
 10 thereof.

Another embodiment of the invention is directed to compounds of the
 formula:



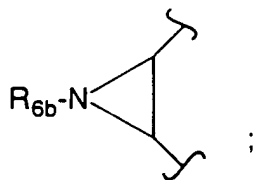
(III)



(IV)

wherein

- 15 E₁ is -(CR₁R₁)_mW₁;
 G₁ is N₃, -CN, -OH, -OR_{6a}, -NO₂, or -(CR₁R₁)_mW₂;
 T₁ is -NR₁W₃, a heterocycle, or is taken together with U₁ or G₁ to form
 a group having the structure



- 20 U₁ is H or -X₁W₆ and, if -X₁W₆, then U₁ is a branched chain;
 J₁ and J_{1a} are independently R₁, Br, Cl, F, I, CN, NO₂ or N₃;
 J₂ and J_{2a} are independently H or R₁;
 R₁ is independently H or alkyl of 1 to 12 carbon atoms;
 R₂ is independently R₃ or R₄ wherein each R₄ is independently
 25 substituted with 0 to 3 R₃ groups;
 R₃ is independently F, Cl, Br, I, -CN, N₃, -NO₂, -OR_{6a}, -OR₁, -N(R₁)₂,
 -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, -SR_{6a}, -S(O)R₁, -S(O)₂R₁, -S(O)OR₁, -S(O)OR_{6a},
 -S(O)₂OR₁, -S(O)₂OR_{6a}, -C(O)OR₁, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R₁,

- $-N(R_1)(C(O)R_1)$, $-N(R_{6b})(C(O)R_1)$, $-N(R_1)(C(O)OR_1)$, $-N(R_{6b})(C(O)OR_1)$,
 $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})(R_1)$, $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$,
 $-C(N(R_{6b}))(N(R_1)_2)$, $-C(N(R_1))(N(R_1)(R_{6b}))$, $-C(N(R_{6b}))(N(R_1)(R_{6b}))$,
 $-C(N(R_1))(N(R_{6b})_2)$, $-C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_1)C(N(R_1))(N(R_1)_2)$,
5 $-N(R_1)C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)_2)$,
 $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$,
 $-N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$,
 $-N(R_1)C(N(R_1))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)(R_{6b}))$,
 $-N(R_{6b})C(N(R_1))(N(R_{6b})_2)$, $-N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$,
10 $-N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2)$, $=O$, $=S$, $=N(R_1)$ or $=N(R_{6b})$;

R_4 is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R_5 is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups;

- 15 R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms which is substituted with 0-3 R_3 groups;

R_{6a} is independently H or an ether- or ester-forming group;

- 20 R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

- 25 W_2 is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W_3 is W_4 or W_5 ;

W_4 is R_5 or $-C(O)R_5$, $-C(O)W_5$, $-SO_2R_5$, or $-SO_2W_5$;

- 30 W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

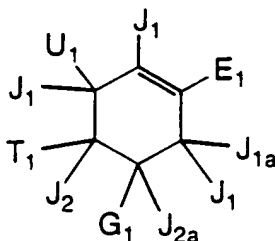
W_6 is $-R_5$, $-W_5$, $-R_{5a}W_5$, $-C(O)OR_{6a}$, $-C(O)R_{6c}$, $-C(O)N(R_{6b})_2$, $-C(NR_{6b})(N(R_{6b})_2)$, $-C(S)N(R_{6b})_2$, or $-C(O)R_2$;

X_1 is a bond, $-O-$, $-N(H)-$, $-N(W_6)-$, $-N(OH)-$, $-N(OW_6)-$, $-N(NH_2)-$, $-N(N(H)(W_6))-$, $-N(N(W_6)_2)-$, $-N(H)N(W_6)-$, $-S-$, $-SO-$, or $-SO_2-$; and

- 35 each m_1 is independently an integer from 0 to 2;

and the salts, solvates, resolved enantiomers and purified diastereomers

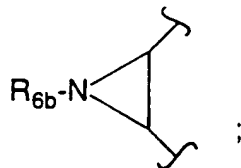
Another embodiment of the invention is directed to compounds of the formula:



(III)

wherein

- 5 E_1 is $-(CR_1R_1)_{m1}W_1$;
 G_1 is N_3 , $-CN$, $-OH$, $-OR_{6a}$, $-NO_2$, or $-(CR_1R_1)_{m1}W_2$;
 T_1 is $-NR_1W_3$, a heterocycle, or is taken together with U_1 or G_1 to form
 a group having the structure



- 10 U_1 is H or $-X_1W_6$;
 J_1 and J_{1a} are independently R_1 , Br, Cl, F, I, CN, NO_2 or N_3 ;
 J_2 and J_{2a} are independently H or R_1 ;
 R_1 is independently H or alkyl of 1 to 12 carbon atoms;
 R_2 is independently R_3 or R_4 wherein each R_4 is independently
 15 substituted with 0 to 3 R_3 groups;
 R_3 is independently F, Cl, Br, I, $-CN$, N_3 , $-NO_2$, $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$,
 $-N(R_1)(R_{6b})$, $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-S(O)R_1$, $-S(O)_2R_1$, $-S(O)OR_1$, $-S(O)OR_{6a}$,
 $-S(O)_2OR_1$, $-S(O)_2OR_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$, $-C(O)OR_{6a}$, $-OC(O)R_1$,
 $-N(R_1)(C(O)R_1)$, $-N(R_{6b})(C(O)R_1)$, $-N(R_1)(C(O)OR_1)$, $-N(R_{6b})(C(O)OR_1)$,
 20 $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})(R_1)$, $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$,
 $-C(N(R_{6b}))(N(R_1)_2)$, $-C(N(R_1))(N(R_1)(R_{6b}))$, $-C(N(R_{6b}))(N(R_1)(R_{6b}))$,
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 $-N(R_1)C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)_2)$,
 $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$,
 25 $-N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$,
 $-N(R_1)C(N(R_1))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)(R_{6b}))$,

$-N(R_{6b})C(N(R_1))(N(R_{6b})_2)$, $-N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$,
 $-N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2)$, $=O$, $=S$, $=N(R_1)$ or $=N(R_{6b})$;

R_4 is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

5 R_5 is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms which is substituted with 0-3 R_3 groups;

10 R_{6a} is independently H or an ether- or ester-forming group;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

15 W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W_2 is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W_3 is W_4 or W_5 ;

20 W_4 is R_5 or $-C(O)R_5$, $-C(O)W_5$, $-SO_2R_5$, or $-SO_2W_5$;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

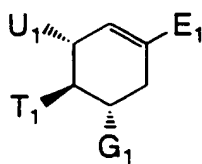
W_6 is $-R_5$, $-W_5$, $-R_{5a}W_5$, $-C(O)OR_{6a}$, $-C(O)R_{6c}$, $-C(O)N(R_{6b})_2$, $-C(NR_{6b})(N(R_{6b})_2)$, $-C(S)N(R_{6b})_2$, or $-C(O)R_2$;

25 X_1 is $-O-$, $-N(H)-$, $-N(W_6)-$, $-N(OH)-$, $-N(OW_6)-$, $-N(NH_2)-$, $-N(N(H)(W_6))-$, $-N(N(W_6)_2)-$, $-N(H)N(W_6)-$, $-S-$, $-SO-$, or $-SO_2-$; and

each m_1 is independently an integer from 0 to 2;

and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

30 Another embodiment of the invention is directed to compounds of the formula:



wherein:

E_1 is $-\text{CO}_2\text{R}_1$;

G_1 is $-\text{NH}_2$, $-\text{N}(\text{H})(\text{R}_5)$ or $-\text{N}(\text{H})(\text{C}(\text{N}(\text{H}))(\text{NH}_2))$;

T_1 is $-\text{N}(\text{H})(\text{C}(\text{O})\text{CH}_3)$;

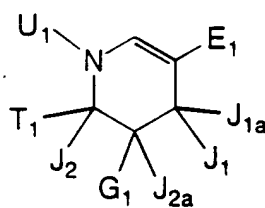
5 U_1 is $-\text{OR}_{60}$;

R_1 is H or an alkyl of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms; and

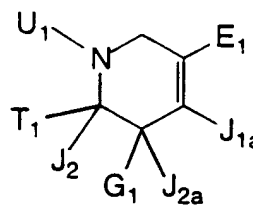
R_{60} is a branched alkyl of 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms;

and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

10 Another embodiment of the invention is directed to compounds of formulas (VII) or (VIII):



(VII)



(VIII)

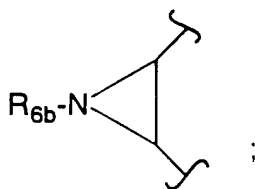
15

wherein

E_1 is $-(\text{CR}_1\text{R}_1)_{m1}\text{W}_1$;

20 G_1 is N_3 , $-\text{CN}$, $-\text{OH}$, $-\text{OR}_{6a}$, $-\text{NO}_2$, or $-(\text{CR}_1\text{R}_1)_{m1}\text{W}_2$;

T_1 is $-\text{NR}_1\text{W}_3$, a heterocycle, or is taken together with G_1 to form a group having the structure



25

U_1 is $-\text{X}_1\text{W}_6$;

J_1 and J_{1a} are independently R_1 , Br , Cl , F , I , CN , NO_2 or N_3 ;

J₂ and J_{2a} are independently H or R₁;

R₁ is independently H or alkyl of 1 to 12 carbon atoms;

R₂ is independently R₃ or R₄ wherein each R₄ is independently substituted with 0 to 3 R₃ groups;

- 5 R₃ is independently F, Cl, Br, I, -CN, N₃, -NO₂, -OR_{6a}, -OR₁, -N(R₁)₂, -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, -SR_{6a}, -S(O)R₁, -S(O)₂R₁, -S(O)OR₁, -S(O)OR_{6a}, -S(O)₂OR₁, -S(O)₂OR_{6a}, -C(O)OR₁, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R₁, -N(R₁)(C(O)R₁), -N(R_{6b})(C(O)R₁), -N(R₁)(C(O)OR₁), -N(R_{6b})(C(O)OR₁), -C(O)N(R₁)₂, -C(O)N(R_{6b})(R₁), -C(O)N(R_{6b})₂, -C(NR₁)(N(R₁)₂),
- 10 -C(N(R_{6b}))(N(R₁)₂), -C(N(R₁))(N(R₁)(R_{6b})), -C(N(R_{6b}))(N(R₁)(R_{6b})), -C(N(R₁))(N(R_{6b})₂), -C(N(R_{6b}))(N(R_{6b})₂), -N(R₁)C(N(R₁))(N(R₁)₂), -N(R₁)C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)₂), -N(R_{6b})C(N(R₁))(N(R₁)₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)₂), -N(R_{6b})C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)(R_{6b})),
- 15 -N(R₁)C(N(R₁))(N(R_{6b})₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)(R_{6b})), -N(R_{6b})C(N(R₁))(N(R_{6b})₂), -N(R₁)C(N(R_{6b}))(N(R_{6b})₂), -N(R_{6b})C(N(R_{6b}))(N(R_{6b})₂), =O, =S, =N(R₁) or =N(R_{6b});

R₄ is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

- 20 R₅ is independently R₄ wherein each R₄ is substituted with 0 to 3 R₃ groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R₃ groups;

- 25 R_{6a} is independently H or a protecting group for hydroxyl or thio;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

- 30 W₁ is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W₂ is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W₃ is W₄ or W₅;

W₄ is R₅ or -C(O)R₅, -C(O)W₅, -SO₂R₅, or -SO₂W₅;

- 35 W₅ is carbocycle or heterocycle wherein W₅ is independently substituted with 0 to 3 R₂ groups;

W₆ is -R₅, -W₅, -R_{5a}W₅, -C(O)OR_{6a}, -C(O)R_{6c}, -C(O)N(R_{6b})₂,
-C(NR_{6b})(N(R_{6b})₂), -C(NR_{6b})(N(H)(R_{6b})), -C(N(H)(N(R_{6b})₂), -C(S)N(R_{6b})₂, or
-C(O)R₂;

X₁ is a bond, -O-, -N(H)-, -N(W₆)-, -S-, -SO-, or -SO₂-; and

5 each m₁ is independently an integer from 0 to 2;
provided, however, that compounds are excluded wherein U₁ is H or
-CH₂CH(OH)CH₂(OH);

and the salts, solvates, resolved enantiomers and purified diastereomers
thereof.

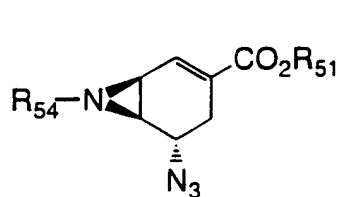
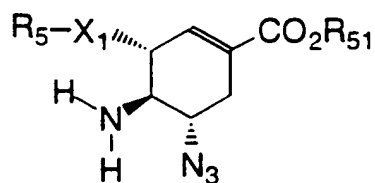
10 In another embodiment of the invention a compound or composition of
the invention is provided that further comprises a pharmaceutically-
acceptable carrier.

In another embodiment of the invention the activity of neuraminidase is
inhibited by a method comprising the step of treating a sample suspected of
15 containing neuraminidase with a compound or composition of the
invention.

Another embodiment of the invention provides a method for inhibiting
the activity of neuraminidase comprising the step of contacting a sample
suspected of containing neuraminidase with the composition embodiments
20 of the invention.

Another embodiment of this invention is a method for the treatment or
prophylaxis of viruses, particularly influenza virus infection in a host
comprising administration to the host, by a route other than topically to the
respiratory tract, of a therapeutically effective dose of an antivirally active
25 compound described in WO 91/16320, WO 92/06691 or US patent 5,360,817.

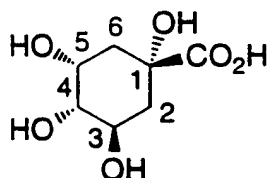
In other embodiments, novel methods for synthesis of the compounds of
this invention are provided. In one such embodiment, a method is provided
for using a compound of the formula 281 wherein the method comprises
treating compound 281 with a compound of the formula R₅-X₁-H to form a
30 compound of the formula 281.1

**281****281.1**

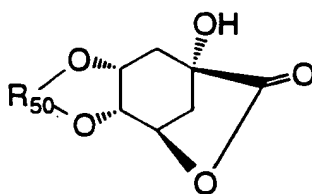
wherein:

- 5 X_1 and R_5 are as described above;
 R_{51} is an acid stable protecting group for a carboxylic acid; and
 R_{54} aziridine activating group.

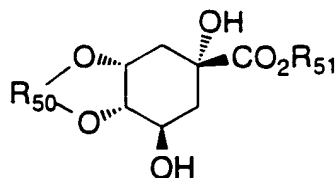
10 In another embodiment, a method is provided for using a compound
 of the formula:

**Quinic Acid**

 wherein the method comprises treating Quinic acid with a geminal
 dialkoxyalkane or geminal dialkoxy cycloalkane and acid to form a compound
 15 of the formula:

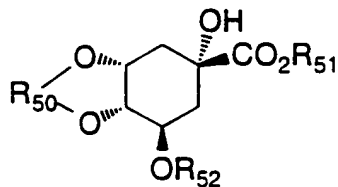
**274**

 treating compound 274 with a metal alkoxide and an alkanol to form a
 compound of the formula:



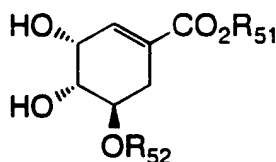
275

treating compound 275 with a sulfonic acid halide and an amine to form a compound of the formula:



276

- 5 treating compound 276 with a dehydrating agent followed by an acid and an alkanol to form a compound of the formula:



272

wherein:

- 10 R50 is a 1,2 diol protecting group;
R51 is an acid stable carboxylic acid protecting group; and
R52 is a hydroxy activating group.

Brief Description of the Drawings

15

Figs. 1 and 2 depict the arterial oxygen saturation (SaO₂) levels of influenza-A infected mice treated with varying i.p. doses of GG167 (4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid), a known anti-influenza compound (Fig. 1) and compound 203 of this invention (Fig. 2): 50, 10, 2 and 0.5 mpk (mg/kg/day) of test compounds and saline control are designated, respectively, by squares, solid circles, triangles, diamonds and open circles. In all Figures, *P<0.05, **P<0.01 compared to the saline controls.

Figs. 3-5 compare the SaO₂ levels achieved in influenza A infected mice treated with p.o. doses of ribavirin (triangles), compound 203 (squares) and GG167 (solid circles); saline controls are open circles: Fig. 3: 150 mpk of each of compound 203 and GG167, 100 mpk ribavirin; Fig. 4: 50 mpk of each of compound 203 and GG167, 32 mpk of ribavirin; Fig. 5: 10 mpk of each of compound 203 and GG167, 10 mpk of ribavirin.

Figs. 6-8 depict the SaO₂ levels in influenza A infected mice treated with low p.o. doses of compounds 262 (circles) and 260 (solid squares) and GG167 (triangles); saline controls are open circles and uninfected controls are open squares: Fig. 6: 1 mpk of each of the test compounds; Fig. 7: 1 mpk of each test compound; Fig. 8: 0.1 mpk of each test compound.

Detailed Description

Compositions of the Invention.

The compounds of this invention exclude compounds heretofore known. However, as will be further apparent below in other embodiments it is within the invention to use for antiviral purposes known compounds heretofore only produced and used as intermediates in the preparation of antiviral compounds. With respect to the United States, the compounds or compositions herein exclude compounds that are anticipated under 35 USC §102 or obvious under 35 USC §103. In particular, the claims herein shall be construed as excluding the compounds which are anticipated by or not possessing novelty over WO 91/16320, WO 92/06691, US patent 5,360,817 or Chandler, M.; *et al.*; *J. Chem. Soc. Perkin Trans. 1*, 1995, 1189-1197.

The foregoing notwithstanding, in an embodiment of the invention one identifies compounds that may fall within the generic scope of WO 91/16320, WO 92/06691, or US patent 5,360,817 but which have (a) formula Ia of the '320 application, (b) carbon for group "A" in the '320 application, and (c) R⁵ of the '320 and '691 applications being "-CH₂YR⁶", "-CHYR⁶CH₂YR⁶" or "-CHYR⁶CHYR⁶CH₂YR⁶" where YR⁶ cannot be either OH or protected OH in which the protecting group is capable of hydrolysis to yield the free OH under conditions of the human gastrointestinal tract, i.e. the compounds are stable to hydrolysis in the gastrointestinal tract. Thus, typically excluded from this embodiment are compounds of the '320 or '691 applications where R⁵ therein is acetyl or other carbacyl having 1-4 carbon atoms.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or
 5 gastric juice upon incubation for 1 hour at 37°C. Such compounds are suitable for use in this embodiment. Note that simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. Prodrugs typically will be stable in the digestive system but are substantially hydrolyzed to the parental drug in the digestive system,
 10 liver or other metabolic organ, or within cells in general.

It should be understood, however, that other embodiments of this invention more fully described below contemplate the use of compounds that are in fact specifically disclosed in WO 91/16320, WO 92/06691, or US patent 5,360,817, including those in which YR⁶ is free hydroxyl, or hydroxyl protected
 15 by a readily hydrolyzable group such as acetyl. In this instance, however, the compounds are delivered by novel routes of administration.

In another embodiment, the compounds herein exclude those in which

(a) E₁ is -CO₂H, -P(O)(OH)₂, -NO₂, -SO₂H, -SO₃H, tetrazolyl, -CH₂CHO, -CHO, or -CH(CHO)₂;
 20

(b) G₁ is -CN, N₃, -NHR₂₀, NR₂₀, -OR₂₀, guanidino, SR₂₀, -N(R₂₀)→O, -N(R₂₀)(OR₂₀), -N(H)(R₂₀)N(R₂₀)₂, unsubstituted pyrimidinyl, or unsubstituted (pyrimidinyl)methyl;

(c) T₁ is -NHR₂₀, -NO₂; and R₂₀ is H; an acyl group having 1 to 4
 25 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; an allyl group or an unsubstituted aryl group or an aryl substituted by a halogen, an OH group, an NO₂ group, an NH₂ group or a COOH group;

(d) each J₁ is H; and

(e) X₁ is a bond, -CH₂- or -CH₂CH₂-;
 30

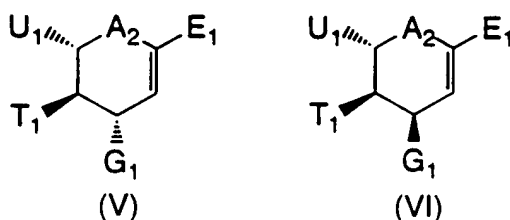
in which case W₆ is not H, W₇ or -CH₂W₇ wherein W₇ is H, -OR_{6a}, -OR₁, -N(R₁)₂, -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, or -SR_{6a}.

In a further embodiment, the compounds of this invention are those in which U₁ is not -CH₂OH, -CH₂OAc, or -CH₂OCH₂Ph.

35 In a further embodiment, the compounds of this invention are those in which E₁ is not -CH₂OH, -CH₂OTMS, or -CHO.

In a further embodiment, the compounds of this invention are those in which U_1 is not bonded directly to the nuclear ring by a carbon atom or U_1 is not substituted with hydroxyl or hydroxyester, in particular U_1 is not polyhydroxyalkane, especially $-\text{CH}(\text{OH})\text{CH}(\text{OH})\text{CH}_2\text{OH}$. In a further
 5 embodiment, U_1 is a branched chain group R_5 as described below or a carbocycle which is substituted with at least one group R_5 .

In a further embodiments, excluded from the invention are compounds of the formula:



wherein:

1. In formula (V):

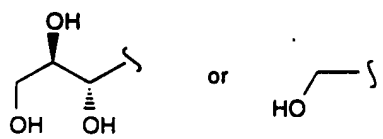
A_2 is $-\text{O}-$ or $-\text{CH}_2-$;

E_1 is $-\text{CO}_2\text{H}$;

G_1 is $-\text{N}(\text{H})(\text{C}(\text{NH})(\text{NH}_2))$;

T_1 is $-\text{N}(\text{H})(\text{Ac})$; and

U_1 is of the formula:



2. In formula (V):

A_2 is $-\text{O}-$ or $-\text{CH}_2-$;

E_1 is $-\text{CO}_2\text{H}$;

G_1 is $-\text{NH}_2$;

T_1 is $-\text{N}(\text{H})(\text{Ac})$; and

U_1 is $-\text{CH}_2\text{OH}$;

3. In formula (V):

A_2 is $-\text{CH}_2-$;

E_1 is $-\text{CH}_2\text{OH}$ or $-\text{CH}_2\text{OTMS}$;

G_1 is $-\text{N}_3$;

T_1 is $-\text{N}(\text{H})(\text{Ac})$; and

U_1 is $-\text{CH}_2\text{OCH}_2\text{Ph}$;

4. In formula (V):
A₂ -CH₂-;
E₁ is -CO₂H or -CO₂CH₃;
G₁ is -N₃;
5 T₁ is -N(H)(Ac); and
U₁ is -CH₂OH;
5. In formula (V):
A₂ -CH₂-;
E₁ is -CO₂H, -CHO, or -CH₂OH;
10 G₁ is -N₃;
T₁ is -N(H)(Ac); and
U₁ is -CH₂OCH₂Ph;
6. In formula (VI):
A₂ -CH₂-;
15 E₁ is -CO₂H;
G₁ is -OCH₃;
T₁ is -NH₂; and
U₁ is -CH₂OH; and
7. In formula (VI):
20 A₂ -CH₂-;
E₁ is -CO₂H;
G₁ is -OCH₃;
T₁ is -N(H)(Ac); and
U₁ is -CH₂OAc.
- 25 Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R₁" or "R_{6a}", then it will be understood that the groups may be the same or different, i.e., each group is independently selected.
- 30 "Heterocycle" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem.
- 35 Soc.", 82:5566 (1960).

Examples of heterocycles include by way of example and not limitation pyridyl, thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, 5 quinoliny, isoquinoliny, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinoliny, tetrahydroisoquinoliny, decahydroquinoliny, octahydroisoquinoliny, azociny, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, 10 xanthenyl, phenoxathiinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indoliziny, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinoliziny, phthalazinyl, naphthyridinyl, quinoxaliny, quinazoliny, cinnoliny, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carboliny, phenanthridinyl, acridinyl, pyrimidinyl, phenanthroliny, phenazinyl, 15 phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazoliny, piperazinyl, indoliny, isoindoliny, quinuclidiny, morpholiny, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazoliny, and isatinoyl.

By way of example and not limitation, carbon bonded heterocycles are 20 bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or 25 isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl. 30

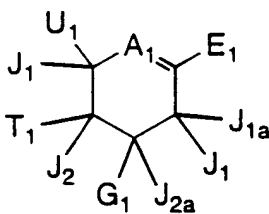
By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, 35 piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or

isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedy, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

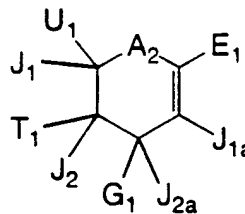
"Alkyl" as used herein, unless stated to the contrary, is C₁-C₁₂

- 5 hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (η -Pr, η -propyl, -CH₂CH₂CH₃), 2-propyl (i -Pr, i -propyl, -CH(CH₃)₂), 1-butyl (η -Bu, η -butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (i -Bu, i -butyl, -CH₂CH(CH₃)₂), 2-butyl (ζ -Bu, ζ -butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (t -Bu, t -butyl, -C(CH₃)₃), 1-pentyl (η -pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃). Examples of
- 20 alkyl groups appear in Table 2 as groups 2-5, 7, 9, and 100-399.

The compositions of the invention comprise compounds of either formula:



(I)



(II)

- 25 In the typical embodiment, the compounds of Formula I are chosen. J₁ and J_{1a} are independently R₁, Br, Cl, F, I, CN, NO₂ or N₃, typically R₁ or F, more typically H or F, more typically yet H. J₂ and J_{2a} are independently H or R₁, typically H. A₁ is -C(J₁)=, or -N=, typically -C(J₁)=, more typically -CH=.
- 30 A₂ is -C(J₁)₂-, -N(J₁)-, -N(O)(J₁)-, -N(O)=, -S-, -S(O)-, -S(O)₂- or -O-, typically -C(J₁)₂-, -N(J₁)-, -S-, or -O-, more typically -C(J₁)₂-, or -O-, more typically yet -CH₂- or -O-, still more typically -CH₂-.

E_1 is $-(CR_1R_1)_{m_1}W_1$.

Typically, R_1 is H or alkyl of 1 to 12 carbon atoms, usually H or an alkyl of 1 to 4 or 5 to 10 carbon atoms, still more typically, H or an alkyl of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms, more typically yet, H or an alkyl of 1 to 3 carbon atoms selected from methyl, ethyl, *n*-propyl, and *i*-propyl. Most typically R_1 is H.

m_1 is an integer of 0 to 2, typically 0 or 1, most typically 0.

m_2 is an integer of 0 to 1.

m_3 is an integer of 1 to 3.

W_1 is a group comprising an acidic hydrogen, a protected acidic group or an R_{6c} amide of the group comprising an acidic hydrogen which, within the context of the invention, means a group having a hydrogen atom that can be removed by a base yielding an anion or its corresponding salt or solvate.

The general principles of acidity and basicity of organic materials are well understood and are to be understood as defining W_1 . They will not be

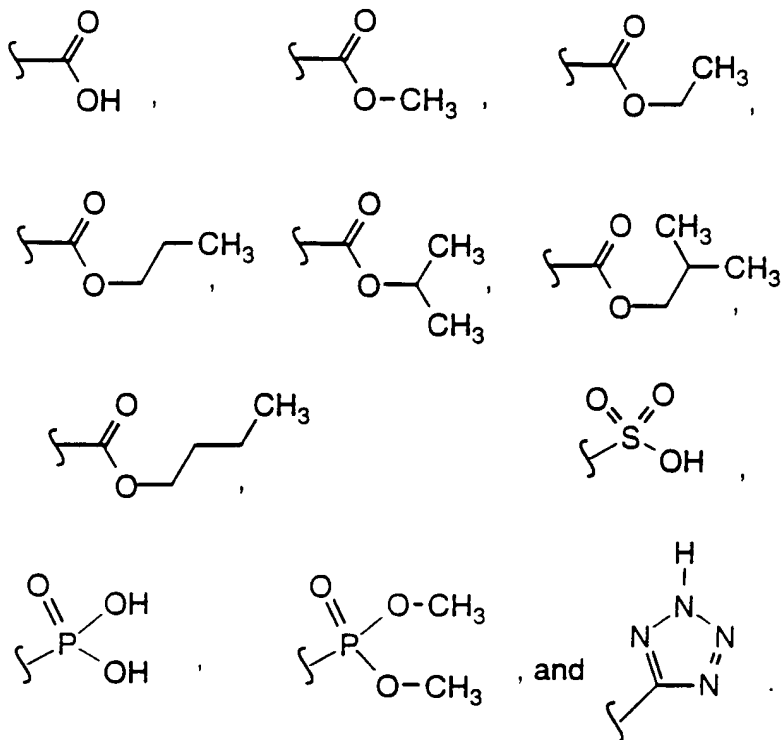
detailed here. However, a description appears in Streitwieser, A.; and Heathcock, C. H.; "Introduction to Organic Chemistry, Second Edition"

(Macmillan, New York, 1981), pages 60-64. Generally, acidic groups of the invention have pK values less than that of water, usually less than $pK = 10$,

typically less than $pK = 8$, and frequently less than $pK = 6$. They include tetrazoles and the acids of carbon, sulfur, phosphorous and nitrogen, typically the carboxylic, sulfuric, sulfonic sulfinic, phosphoric and phosphonic acids, together with the R_{6c} amides and R_{6b} esters of those acids (R_{6a} and R_{6c} are defined below). Exemplary W_1 are $-CO_2H$, $-CO_2R_{6a}$, $-OSO_3H$, $-SO_3H$, $-SO_2H$, $-OPO_3H_2$, $-PO_3(R_{6a})_2$, $-PO_3H_2$, $-PO_3(H)(R_{6a})$, and $-OPO_3(R_{6a})_2$. W_1 typically is E_1 , and E_1 typically is $-CO_2H$, $-CO_2R_{6a}$, $-CO_2R_4$ or CO_2R_1 , and most typically is CO_2R_{14} wherein R_{14} is normal or terminally secondary C_1 - C_6 alkyl.

W_1 may also be a protected acidic group, which, within the context of the invention means an acidic group as described above that has been protected by one of the groups commonly used in the art for such groups and are described below under R_{6a} . More typically, protected W_1 is $-CO_2R_1$, $-SO_3R_1$, $-S(O)OR_1$, $-P(O)(OR_1)_2$, $-C(O)NHSO_2R_4$, or $-SO_2NHC(O)-R_4$, wherein R_1 is defined above.

Most typically, E_1 is selected from $-C(O)O(CH_2)_bCH((CH_2)_cCH_3)_2$ where $b = 0$ to 4, $c = 0$ to 4, and $b + c = 1$ to 4, or from the group of



Exemplary E1 groups are listed in Tables 3a through 3b.

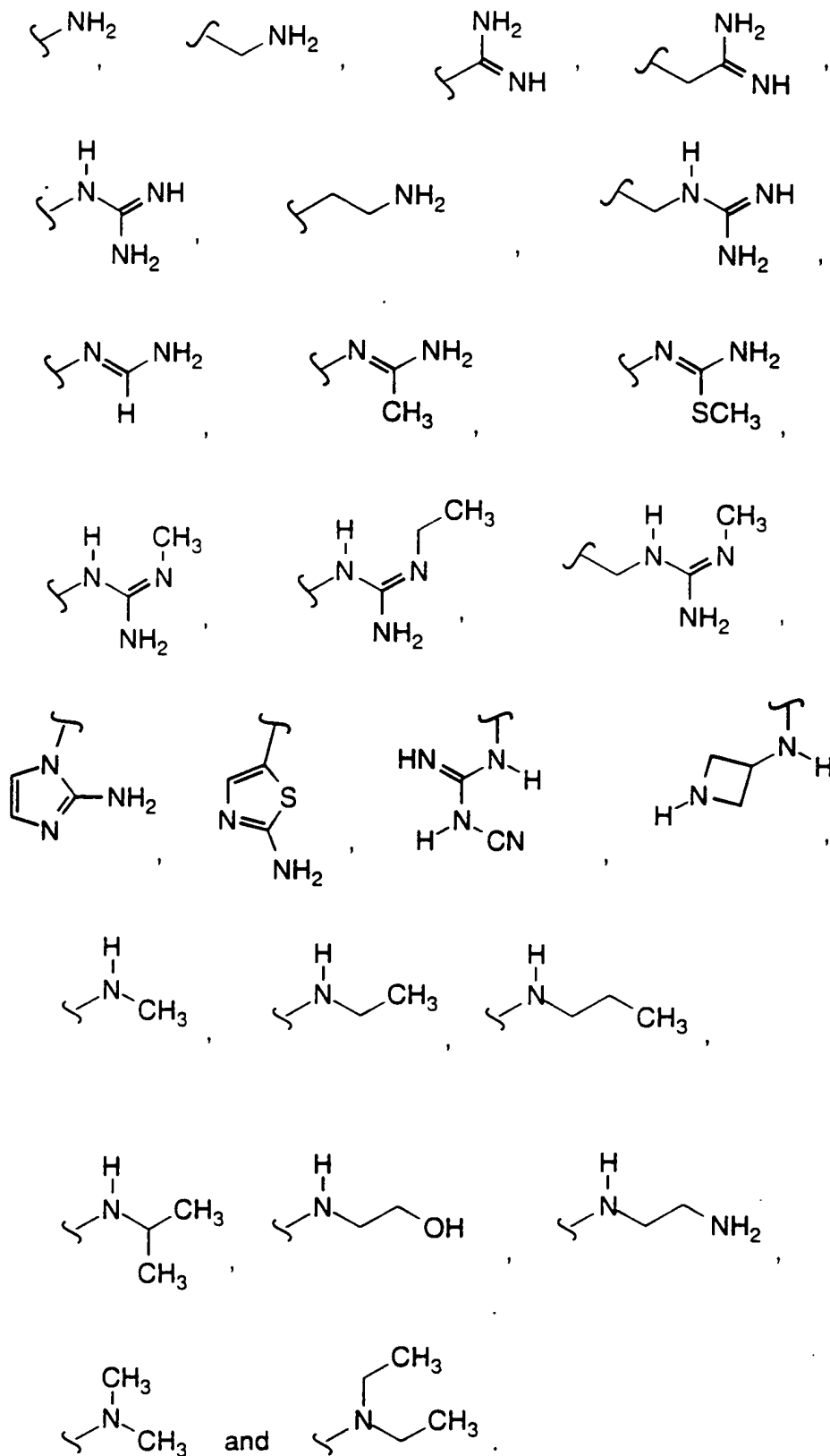
G1 is N3, -CN, -OH, OR_{6a}, -NO₂ or -(CR₁R₁)_{m1}W₂, wherein R₁ and m₁ are defined above. Ordinarily, G₁ is -(CR₁R₁)_{m1}W₂.

- 5 W₂ is a group comprising a basic heteroatom, a protected basic heteroatom or an R_{6b} amide of the basic heteroatom. W₂ generally comprises a basic heteroatom, which, within the context of the invention means an atom other than carbon which is capable of protonation, typically by an acidic hydrogen having an acidity in the range described above for W₁. The basic
- 10 principles of basicity are described in Streitwieser and Heathcock (*op. cit.*) and provide meaning for the term basic heteroatom as will be understood by those ordinarily skilled in the art. Generally, the basic heteroatoms employed in the compounds of the invention have pK values for the corresponding protonated form that are in the range of values described above for W₁. Basic
- 15 heteroatoms include the heteroatoms common in organic compounds which have an un-shared, non-bonding, n-type, or the like, electron pair. By way of example and not limitation, typical basic heteroatoms include the oxygen, nitrogen, and sulfur atoms of groups such as alcohols, amines, amidines, guanidines, sulfides, and the like, frequently, amines, amidines and
- 20 guanidines. Ordinarily, W₂ is amino or an amino alkyl (generally lower alkyl) group such as aminomethyl, aminoethyl or aminopropyl; an amidinyl,

or an amidinoalkyl group such as amidinomethyl, amidinoethyl, or amidinopropyl; or guanidiny, or a guanidinoalkyl group such as guanidinomethyl, guanidinoethyl, or guanidinopropyl (in each instance wherein the alkyl group serves to bridge the basic substituent to the carbocyclic ring). More typically, W₂ is amino, amidino, guanidino, heterocycle, heterocycle substituted with 1 or 2 amino or guanidino groups (usually 1), or an alkyl of 2 to 3 carbon atoms substituted with amino or guanidino, or such alkyl substituted with an amino and a second group selected from the group consisting of hydroxy and amino. The heterocycles useful as W₂ include typically N or S-containing 5 or 6 membered rings, wherein the ring contains 1 or 2 heteroatoms. Such heterocycles generally are substituted at ring carbon atoms. They may be saturated or unsaturated and may be linked to the core cyclohexene by lower alkyl (m₁=1 or 2) or by -NR₁-. Still more typically, W₂ is -NHR₁, -C(NH)(NH₂), -NR₁-C(NR₁)(NR₁R₃), -NH-C(NH)(NHR₃), -NH-C(NH)(NHR₁), -NH-C(NH)NH₂, -CH(CH₂NHR₁)(CH₂OH), -CH(CH₂NHR₁)(CH₂NHR₁), -CH(NHR₁)-(CR₁R₁)_{m2}-CH(NHR₁)R₁, -CH(OH)-(CR₁R₁)_{m2}-CH(NHR₁)R₁, or -CH(NHR₁)-(CR₁R₁)_{m2}-CH(OH)R₁, -(CR₁R₁)_{m2}-S-C(NH)NH₂, -N=C(NHR₁)(R₃), -N=C(SR₁)N(R₁)₂, -N(R₁)C(NH)N(R₁)C=N, or -N=C(NHR₁)(R₁); wherein each m₂ is ordinarily 0, and ordinarily R₁ is H and R₃ is C(O)N(R₁)₂.

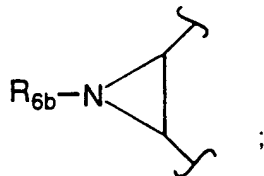
W₂ optionally is a protected basic heteroatom which within the context of the invention means a basic heteroatom as described above that has been protected by R_{6b} such as one of the groups common in the art. Such groups are described in detail in Greene (*op. cit.*) as set forth below. Such groups include by way of example and not limitation, amides, carbamates, amino acetals, imines, enamines, N-alkyl or N-aryl phosphiny, N-alkyl or N-aryl sulfinyls or sulfonyls, N-alkyl or N-aryl silyls, thioethers, thioesters, disulfides, sulfinyls, and the like. In some embodiments, the protecting group R_{6b} will be cleavable under physiological conditions, typically it will be cleavable *in vivo* where, for example, the basic heteroatom forms an amide with an organic acid or an amino acid such as a naturally occurring amino acid or a polypeptide as described below for the R_{6a} group.

Typically G₁ is selected from the group consisting of:



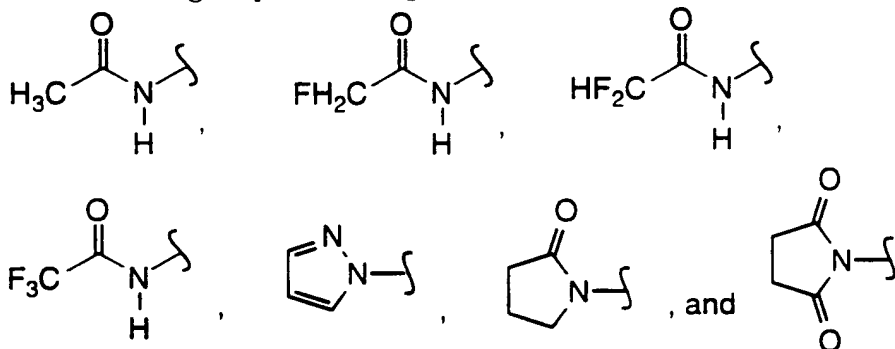
Further exemplary G₁ groups are listed in Table 4.

T₁ is -NR₁W₃ or heterocycle, or is taken together with U₁ or G₁ to form a group having the structure



5

where R_{6b} is defined below, and R₁ and W₃ are defined above. Generally T₁ is selected from the group consisting of:



Exemplary T₁ groups are listed in Table 5.

10 W₃ is W₄ or W₅, wherein W₄ is R₁ or -C(O)R₅, -C(O)W₅, -SO₂R₅, or -SO₂W₅. Typically, W₃ is -C(O)R₅ or W₅.

R₂ is independently R₃ or R₄ as defined below, with the proviso that each R₄ is independently substituted with 0 to 3 R₃ groups;

R₃ is independently F, Cl, Br, I, -CN, N₃, -NO₂, -OR_{6a}, -OR₁, -N(R₁)₂,
 15 -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, -SR_{6a}, -S(O)R₁, -S(O)₂R₁, -S(O)OR₁, -S(O)OR_{6a},
 -S(O)₂OR₁, -S(O)₂OR_{6a}, -C(O)OR₁, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R₁,
 -N(R₁)(C(O)R₁), -N(R_{6b})(C(O)R₁), -N(R₁)(C(O)OR₁), -N(R_{6b})(C(O)OR₁),
 -C(O)N(R₁)₂, -C(O)N(R_{6b})(R₁), -C(O)N(R_{6b})₂, -C(NR₁)(N(R₁)₂),
 -C(N(R_{6b}))(N(R₁)₂), -C(N(R₁))(N(R₁)(R_{6b})), -C(N(R_{6b}))(N(R₁)(R_{6b})),
 20 -C(N(R₁))(N(R_{6b})₂), -C(N(R_{6b}))(N(R_{6b})₂), -N(R₁)C(N(R₁))(N(R₁)₂),
 -N(R₁)C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)₂),
 -N(R_{6b})C(N(R₁))(N(R₁)₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)₂),
 -N(R_{6b})C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)(R_{6b})),
 -N(R₁)C(N(R₁))(N(R_{6b})₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)(R_{6b})),
 25 -N(R_{6b})C(N(R₁))(N(R_{6b})₂), -N(R₁)C(N(R_{6b}))(N(R_{6b})₂),
 -N(R_{6b})C(N(R_{6b}))(N(R_{6b})₂), =O, =S, =N(R₁) or =N(R_{6b}). Typically R₃ is F, Cl,

-CN, N₃, NO₂, -OR_{6a}, -OR₁, -N(R₁)₂, -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, -SR_{6a}, -C(O)OR₁, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R₁, -NR₁C(O)R₁, -N(R_{6b})C(O)R₁, -C(O)N(R₁)₂, -C(O)N(R_{6b})(R₁), -C(O)N(R_{6b})₂, or =O. More typical R₃ groups comprising R_{6b} include -C(O)N(R_{6b})₂, -C(O)N(R_{6b})(R₁), -C(S)N(R_{6b})₂, or
 5 -C(S)N(R_{6b})(R₁). More typically yet R₃ is F, Cl, -CN, N₃, -OR₁, -N(R₁)₂, -SR₁, -C(O)OR₁, -OC(O)R₁, or =O. More typically still, R₃ is F, -OR₁, -N(R₁)₂, or =O. In the context of the present application, "=O" denotes a double bonded oxygen atom (oxo), and "=S" =N(R_{6b}) and "=N(R₁)" denote the sulfur and nitrogen analogs.

10 R₄ is alkyl of 1 to 12 carbon atoms, and alkynyl or alkenyl of 2 to 12 carbon atoms. The alkyl R₄'s are typically of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms and the alkenyl and alkynyl R₄'s are typically of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms. R₄ ordinarily is alkyl (as defined above). When R₄ is alkenyl it is typically ethenyl (-CH=CH₂), 1-prop-1-enyl (-CH=CHCH₃), 1-
 15 prop-2-enyl (-CH₂CH=CH₂), 2-prop-1-enyl (-C(=CH₂)(CH₃)), 1-but-1-enyl (-CH=CHCH₂CH₃), 1-but-2-enyl (-CH₂CH=CHCH₃), 1-but-3-enyl (-CH₂CH₂CH=CH₂), 2-methyl-1-prop-1-enyl (-CH=C(CH₃)₂), 2-methyl-1-prop-2-enyl (-CH₂C(=CH₂)(CH₃)), 2-but-1-enyl (-C(=CH₂)CH₂CH₃), 2-but-2-enyl (-C(CH₃)=CHCH₃), 2-but-3-enyl (-CH(CH₃)CH=CH₂), 1-pent-1-enyl
 20 (-C=CHCH₂CH₂CH₃), 1-pent-2-enyl (-CHCH=CHCH₂CH₃), 1-pent-3-enyl (-CHCH₂CH=CHCH₃), 1-pent-4-enyl (-CHCH₂CH₂CH=CH₂), 2-pent-1-enyl (-C(=CH₂)CH₂CH₂CH₃), 2-pent-2-enyl (-C(CH₃)=CH₂CH₂CH₃), 2-pent-3-enyl (-CH(CH₃)CH=CHCH₃), 2-pent-4-enyl (-CH(CH₃)CH₂CH=CH₂) or 3-methyl-1-but-2-enyl (-CH₂CH=C(CH₃)₂). More typically, R₄ alkenyl groups are of 2, 3 or
 25 4 carbon atoms. When R₄ is alkynyl it is typically ethynyl (-CCH), 1-prop-1-ynyl (-CCCH₃), 1-prop-2-ynyl (-CH₂CCH), 1-but-1-ynyl (-CCCH₂CH₃), 1-but-2-ynyl (-CH₂CCCH₃), 1-but-3-ynyl (-CH₂CH₂CCH), 2-but-3-ynyl (CH(CH₃)CCH), 1-pent-1-ynyl (-CCCH₂CH₂CH₃), 1-pent-2-ynyl (-CH₂CCCH₂CH₃), 1-pent-3-ynyl (-CH₂CH₂CCCH₃) or 1-pent-4-ynyl (-CH₂CH₂CH₂CCH). More typically,
 30 R₄ alkynyl groups are of 2, 3 or 4 carbon atoms.

R₅ is R₄, as defined above, or R₄ substituted with 0 to 3 R₃ groups. Typically R₅ is an alkyl of 1 to 4 carbon atoms substituted with 0 to 3 fluorine atoms.

35 R_{5a} is alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms which is substituted with 0-3 R₃ groups. As defined above for R₄, R_{5a}'s are of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12

carbon atoms when alkylene and of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms when alkenylene or alkynylene. Each of the typical R₄ groups is a typical R_{5a} group with the proviso that one of the hydrogen atoms of the described R₄ group is removed to form the open valence to a carbon atom through which the second bond to the R_{5a} is attached.

R₁₀ is alkyl, alkenyl, alkynyl of 1 to 12 carbon atoms substituted with 0 to 3 R₂.

R₁₁ is independently H or R₁₀.

R₁₂ is a cycloalkyl of 3 to 10 carbon atoms, or cycloalkenyl of 4 to 10 carbon atoms.

R₁₄ is normal or terminally secondary C₁-C₆ alkyl.

W₅ is a carbocycle or heterocycle, with the proviso that each W₅ is independently substituted with 0 to 3 R₂ groups. W₅ carbocycles and T₁ and W₅ heterocycles are stable chemical structures. Such structures are isolatable in measurable yield, with measurable purity, from reaction mixtures at temperatures from -78°C to 200°C. Each W₅ is independently substituted with 0 to 3 R₂ groups. Typically, T₁ and W₅ are a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. More typically, T₁ or W₅ has 3 to 10 ring atoms, still more typically, 3 to 7 ring atoms, and ordinarily 3 to 6 ring atoms. The T₁ and W₅ rings are saturated when containing 3 ring atoms, saturated or monounsaturated when containing 4 ring atoms, saturated, or mono- or diunsaturated when containing 5 ring atoms, and saturated, mono- or diunsaturated, or aromatic when containing 6 ring atoms.

When W₅ is carbocyclic, it is typically a 3 to 7 carbon monocycle or a 7 to 12 carbon atom bicycle. More typically, W₅ monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. W₅ bicyclic carbocycles have 7 to 12 ring atoms arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, still more typically, 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

A T₁ or W₅ heterocycle is typically a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). More typically, T₁ and W₅

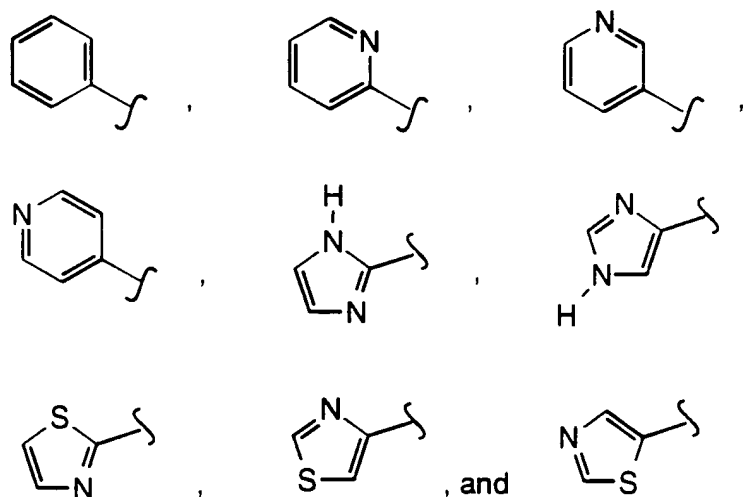
heterocyclic monocycles have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S), still more typically, 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). T₁ and W₅ heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system, still more typically, 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 heteroatoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system.

Typically T₁ and W₅ heterocycles are selected from pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, or pyrrolyl.

More typically, the heterocycle of T₁ and W₅ is bonded through a carbon atom or nitrogen atom thereof. Still more typically T₁ heterocycles are bonded by a stable covalent bond through a nitrogen atom thereof to the cyclohexene ring of the compositions of the invention and W₅ heterocycles are bonded by a stable covalent bond through a carbon or nitrogen atom thereof to the cyclohexene ring of the compositions of the invention. Stable covalent bonds are chemically stable structures as described above.

W₅ optionally is selected from the group consisting of:

20



U₁ is H or -X₁W₆, but typically the latter.

X₁ is a bond, -CR₅R₅-, -(CR₅R₅)₂-, -O-, -N(H)-, -N(W₆)-, -N(OH)-, -N(OW₆)-, -N(NH₂)-, -N(N(H)(W₆))-, -N(N(W₆)₂)-, -N(H)N(W₆)-, -S-, -SO-, or -SO₂-; typically, X₁ is a bond, -CR₅R₅-, -(CR₅R₅)₂-, -O-, -N(H)-, -N(R₅)-, -N(OH)-, -N(OR₅)-, -N(NH₂)-, -N(N(H)(R₅))-, -N(N(R₅)₂)-, -N(H)N(R₅)-, -S-,

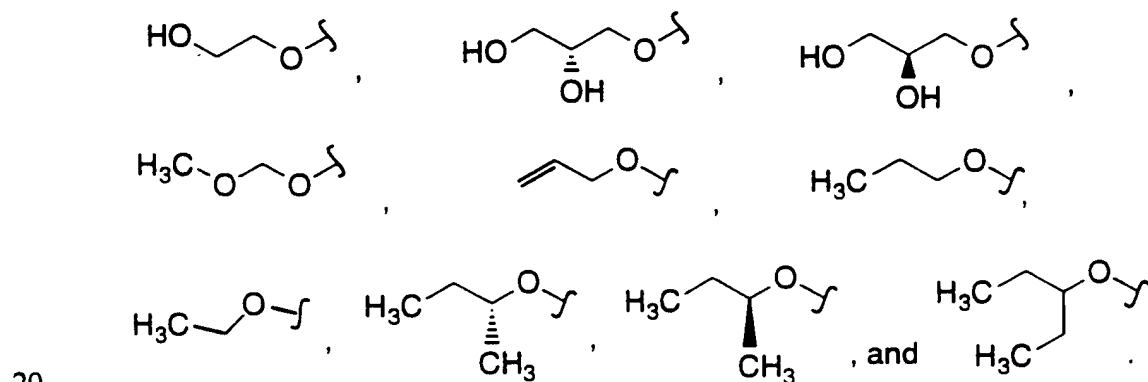
-SO-, or -SO₂-, more typically X₁ is a bond, -CR₁R₁-, -(CR₁R₁)₂-, -O-, -NR₁-, -N(OR₁)-, -N(NR₁R₁)-, -S-, -SO-, or -SO₂-. Ordinarily X₁ is -O-, -NH-, -S-, -SO-, or -SO₂-;

W₆ is -R₅, -W₅, -R_{5a}W₅, -C(O)OR_{6a}, -C(O)R_{6c}, -C(O)N(R_{6b})₂,

- 5 -C(NR_{6b})(N(R_{6b})₂), -C(NR_{6b})(N(H)(R_{6b})), -C(N(H)(N(R_{6b})₂), -C(S)N(R_{6b})₂, or -C(O)R₂, typically is -R₅, -W₅, or -R_{5a}W₅; in some embodiments, W₆ is R₁, -C(O)-R₁, -CHR₁W₇, -CH(R₁)_aW₇, -CH(W₇)₂, (where a is 0 or 1, but is 0 when W₇ is divalent) or -C(O)W₇. In some embodiments, W₆ is -CHR₁W₇ or -C(O)W₇, or W₆ is -(CH₂)_{m1}CH((CH₂)_{m3}R₃)₂, -(CH₂)_{m1}C((CH₂)_{m3}R₃)₃;
 10 -(CH₂)_{m1}CH((CH₂)_{m3}R_{5a}W₅)₂; -(CH₂)_{m1}CH((CH₂)_{m3}R₃)((CH₂)_{m3}R_{5a}W₅); -(CH₂)_{m1}C((CH₂)_{m3}R₃)₂(CH₂)_{m3}R_{5a}W₅, (CH₂)_{m1}C((CH₂)_{m3}R_{5a}W₅)₃ or -(CH₂)_{m1}C((CH₂)_{m3}R₃)((CH₂)_{m3}R_{5a}W₅)₂; and wherein m₃ is an integer from 1 to 3.

- W₇ is R₃ or R₅, but typically is alkyl of 1 to 12 carbons substituted with 0
 15 to 3 R₃ groups, the latter typically selected from the group consisting of -NR₁(R_{6b}), -N(R_{6b})₂, -OR_{6a}, or SR_{6a}. More typically, W₇ is -OR₁ or an alkyl of 3 to 12 carbon atoms substituted with OR₁.

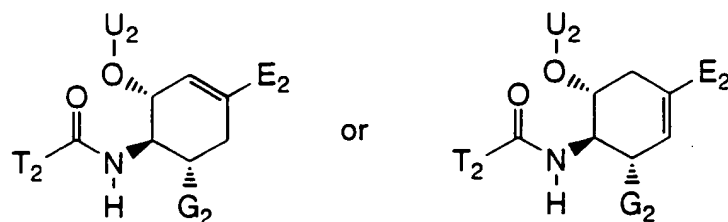
In general, U₁ is R₁O-, -OCHR₁W₇,



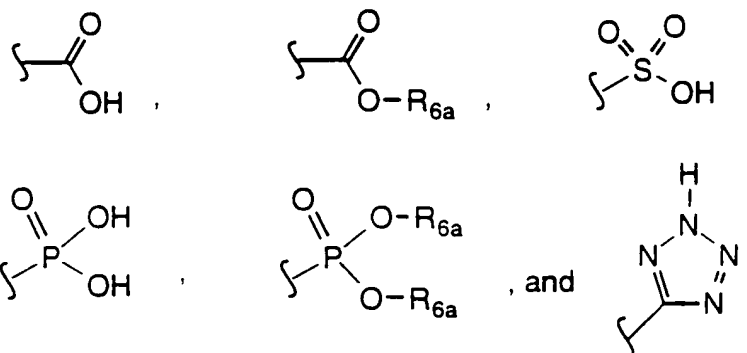
Exemplary U₁ groups are listed in Table 2.

An embodiment of the invention comprises a compound of the
 formula:

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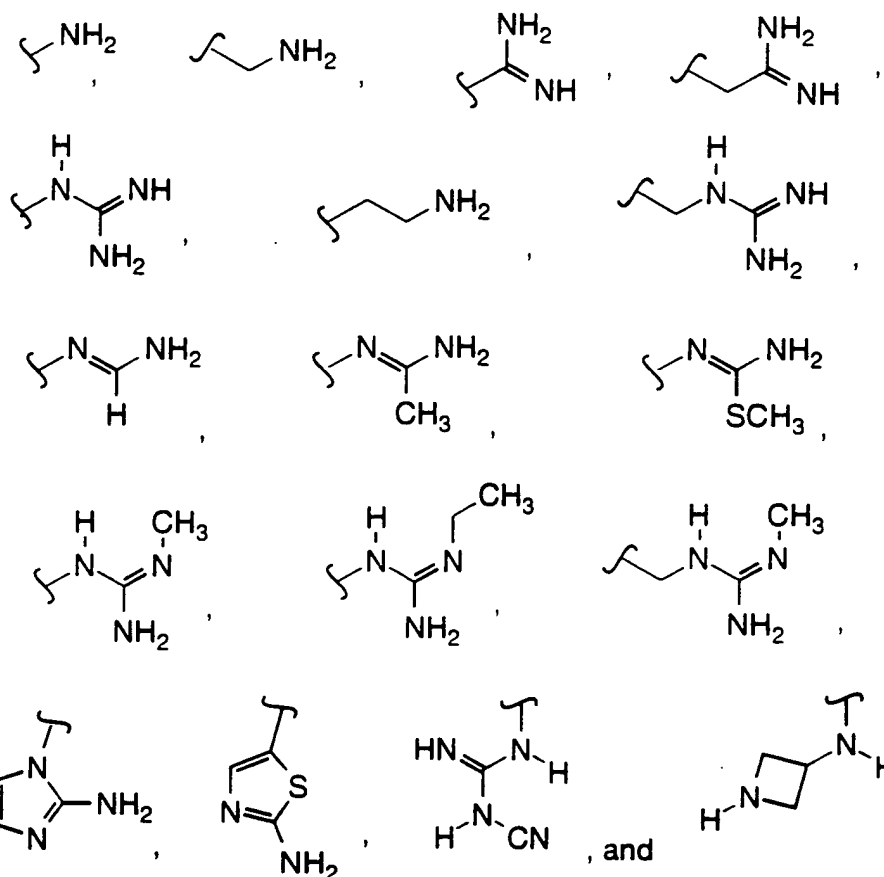


wherein E₂ is E₁, but is typically selected from the group consisting of:



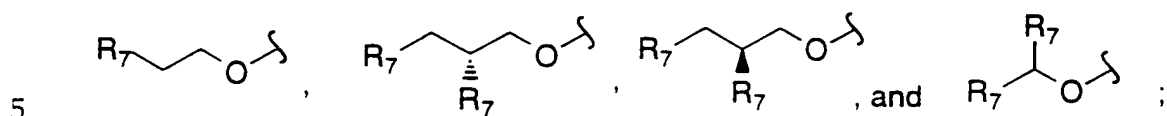
5

and wherein G₂ is G₁, but is typically selected from the group consisting of:



and wherein T₂ is R₄ or R₅. Generally, T₂ is alkyl of 1 to 2 carbon atoms substituted with 0 to 3 fluorine atoms.

U₂ is one of:



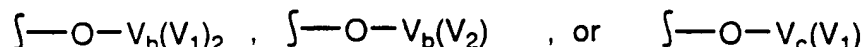
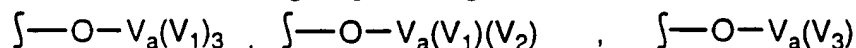
wherein R₇ is H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -OCH₃, -OAc (-O-C(O)CH₃), -OH, -NH₂, or -SH, typically H, -CH₃ or -CH₂CH₃.

Groups R_{6a} and R_{6b} are not critical functionalities and may vary widely.

- 10 When not H, their function is to serve as intermediates for the parental drug substance. This does not mean that they are biologically inactive. On the contrary, a principal function of these groups is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs are absorbed more effectively than
- 15 the parental drug they in fact often possess greater potency *in vivo* than the parental drug. R_{6a} and R_{6b} are removed either *in vitro*, in the instance of

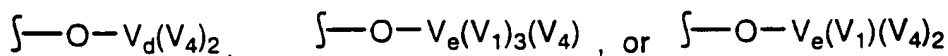
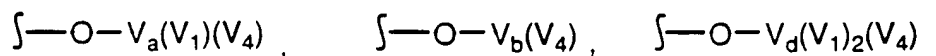
chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting pro-functionality products, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

- 5 R_{6a} is H or an ether- or ester-forming group. "Ether-forming group" means a group which is capable of forming a stable, covalent bond between the parental molecule and a group having the formula:



- Wherein V_a is a tetravalent atom typically selected from C and Si; V_b is a
 10 trivalent atom typically selected from B, Al, N, and P, more typically N and P;
 V_c is a divalent atom typically selected from O, S, and Se, more typically S; V_1
 is a group bonded to V_a , V_b or V_c by a stable, single covalent bond, typically
 V_1 is W_6 groups, more typically V_1 is H, R_2 , W_5 , or $-R_{5a}W_5$, still more
 typically H or R_2 ; V_2 is a group bonded to V_a or V_b by a stable, double
 15 covalent bond, provided that V_2 is not =O, =S or =N-, typically V_2 is =C(V_1)₂
 wherein V_1 is as described above; and V_3 is a group bonded to V_a by a stable,
 triple covalent bond, typically V_3 is $\equiv C(V_1)$ wherein V_1 is as described above.

- "Ester-forming group" means a group which is capable of forming a
 stable, covalent bond between the parental molecule and a group having the
 20 formula:



- Wherein V_a , V_b , and V_1 , are as described above; V_d is a pentavalent atom
 typically selected from P and N; V_e is a hexavalent atom typically S; and V_4 is
 a group bonded to V_a , V_b , V_d or V_e by a stable, double covalent bond,
 25 provided that at least one V_4 is =O, =S or =N- V_1 , typically V_4 , when other
 than =O, =S or =N-, is =C(V_1)₂ wherein V_1 is as described above.

Protecting groups for -OH functions (whether hydroxy, acid or other functions) are embodiments of "ether- or ester-forming groups".

Particularly of interest are ether- or ester-forming groups that are capable of functioning as protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed under R_{6c} below. R_{6c} is capable of protecting hydroxyl or thio groups such that hydrolysis from the parental molecule yields hydroxyl or thio.

In its ester-forming role, R_{6a} typically is bound to any acidic group such as, by way of example and not limitation, a $-CO_2H$ or $-C(S)OH$ group, thereby resulting in $-CO_2R_{6a}$. R_{6a} for example is deduced from the enumerated ester groups of WO 95/07920.

Examples of R_{6a} include

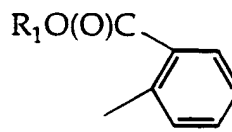
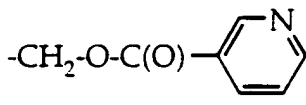
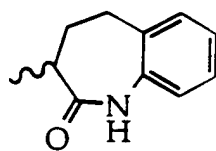
C_3-C_{12} heterocycle (described above) or aryl. These aromatic groups optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl,

C_3-C_{12} heterocycle or aryl substituted with halo, R_1 , $R_1-O-C_1-C_{12}$ alkylene, C_1-C_{12} alkoxy, CN, NO_2 , OH, carboxy, carboxyester, thiol, thioester, C_1-C_{12} haloalkyl (1-6 halogen atoms), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl. Such groups include 2-, 3- and 4-alkoxyphenyl (C_1-C_{12} alkyl), 2-, 3- and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-ethylpiperazinyl, benzyl,

alkylsalicylphenyl (C₁-C₄ alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-,3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl

(-C₁₀H₆-OH) and aryloxy ethyl [C₆-C₉-aryl (including phenoxy ethyl)], 2,2'-dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, -C₆H₄CH₂-

5 N(CH₃)₂, trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C₁₋₄ alkyl);

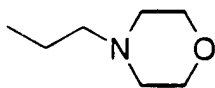


; C₄ - C₈ esters of 2-carboxyphenyl; and C₁-C₄ alkylene-C₃-C₆ aryl (including benzyl, -CH₂-pyrrolyl, -CH₂-thienyl, -CH₂-imidazolyl, -CH₂-oxazolyl, -CH₂-isoxazolyl, -CH₂-thiazolyl, -CH₂-isothiazolyl, -CH₂-pyrazolyl, -CH₂-pyridinyl and -CH₂-pyrimidinyl)

10 substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or groups selected from halogen, C₁-C₁₂ alkoxy (including methoxy and ethoxy), cyano, nitro, OH, C₁-C₁₂ haloalkyl (1 to 6 halogen atoms; including -CH₂-CCl₃), C₁-C₁₂ alkyl (including methyl and ethyl), C₂-C₁₂ alkenyl or C₂-C₁₂ alkynyl;

15 alkoxy ethyl [C₁-C₆ alkyl including -CH₂-CH₂-O-CH₃ (methoxy ethyl)];

alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including -CH₃, -CH(CH₃)₂, -C(CH₃)₃, -CH₂CH₃, -(CH₂)₂CH₃, -(CH₂)₃CH₃, -(CH₂)₄CH₃, -(CH₂)₅CH₃, -CH₂CH₂F, -CH₂CH₂Cl, -CH₂CF₃, and -CH₂CCl₃);



; -N-2-propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, -CH₂-C(O)-N(R¹)₂, -CH₂-S(O)(R¹), -CH₂-S(O)₂(R¹), -CH₂-CH(OC(O)CH₂R¹)-CH₂(OC(O)CH₂R¹), cholesteryl, enolpyruvate (HOOC-C(=CH₂)-), glycerol;

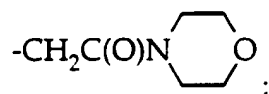
25 a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9 monosaccharide residues);

triglycerides such as α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C₆₋₂₆, C₆₋₁₈ or C₆₋₁₀ fatty acids such as linoleic, lauric, myristic, 30 palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental compounds herein through a glyceryl oxygen of the triglyceride;

phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

phthalidyl (shown in Fig. 1 of Clayton et al., *Antimicrob. Agents Chemo.* 5(6):670-671 [1974]);

- 5 cyclic carbonates such as (5-R_d-2-oxo-1,3-dioxolen-4-yl) methyl esters (Sakamoto et al., *Chem. Pharm. Bull.* 32(6)2241-2248 [1984]) where R_d is R₁, R₄ or aryl; and

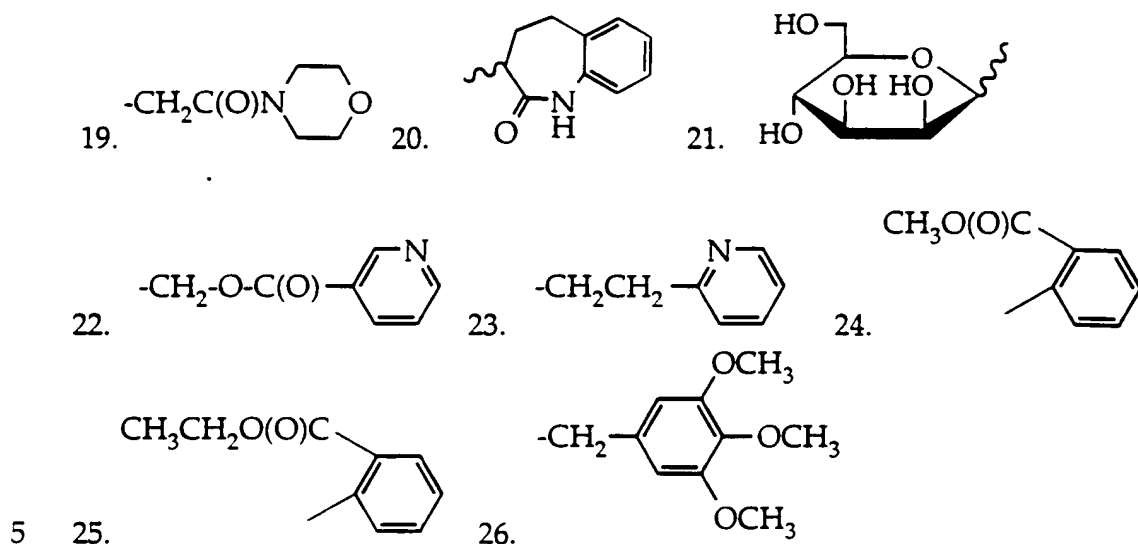


- 10 The hydroxyl groups of the compounds of this invention optionally are substituted with one of groups III, IV or V disclosed in WO94/21604, or with isopropyl.

As further embodiments, Table A lists examples of R_{6a} ester moieties that for example can be bonded via oxygen to -C(O)O- and -P(O)(O-)₂ groups. Several R_{6c} amidates also are shown, which are bound directly to -C(O)- or
 15 -P(O)₂. Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound herein having a free hydroxyl with the corresponding halide (chloride or acyl chloride and the like) and N,N-dicyclohexyl-N-morpholine carboxamidine (or another base such as DBU, triethylamine, CsCO₃, N,N-dimethylaniline and the like) in DMF (or other solvent such as acetonitrile or
 20 N-methylpyrrolidone). When W₁ is phosphonate, the esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with the monochlorophosphonate or dichlorophosphonate (or another
 25 activated phosphonate).

TABLE A

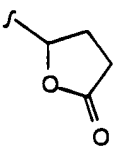
1. -CH ₂ -C(O)-N(R ₁) ₂ *	10. -CH ₂ -O-C(O)-C(CH ₃) ₃
2. -CH ₂ -S(O)(R ₁)	11. -CH ₂ -CCl ₃
3. -CH ₂ -S(O) ₂ (R ₁)	12. -C ₆ H ₅
30 4. -CH ₂ -O-C(O)-CH ₂ -C ₆ H ₅	13. -NH-CH ₂ -C(O)O-CH ₂ CH ₃
5. 3-cholesteryl	14. -N(CH ₃)-CH ₂ -C(O)O-CH ₂ CH ₃
6. 3-pyridyl	15. -NHR ₁
7. N-ethylmorpholino	16. -CH ₂ -O-C(O)-C ₁₀ H ₁₅
8. -CH ₂ -O-C(O)-C ₆ H ₅	17. -CH ₂ -O-C(O)-CH(CH ₃) ₂
35 9. -CH ₂ -O-C(O)-CH ₂ CH ₃	18. -CH ₂ -C#H(OC(O)CH ₂ R ₁)-CH ₂ - -(OC(O)CH ₂ R ₁)*

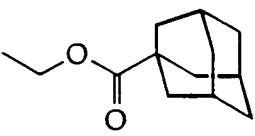


- chiral center is (R), (S) or racemate.

Other esters that are suitable for use herein are described in EP 632,048.

R_{6a} also includes "double ester" forming profunctionalities such as

- 10 $-\text{CH}_2\text{OC}(\text{O})\text{OCH}_3$,  $-\text{CH}_2\text{SCOCH}_3$, $-\text{CH}_2\text{OCON}(\text{CH}_3)_2$, or alkyl- or aryl-acyloxyalkyl groups of the structure $-\text{CH}(\text{R}_1 \text{ or } \text{W}_5)\text{O}((\text{CO})\text{R}_{37})$ or $-\text{CH}(\text{R}_1 \text{ or } \text{W}_5)((\text{CO})\text{OR}_{38})$ (linked to oxygen of the acidic group) wherein R₃₇ and R₃₈ are alkyl, aryl, or alkylaryl groups (see U.S. patent 4,968,788). Frequently R₃₇ and R₃₈ are bulky groups such as branched alkyl, ortho-substituted aryl, meta-
- 15 substituted aryl, or combinations thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful R_{6a} groups are alkylacyloxymethyl esters and their derivatives, including $-\text{CH}(\text{CH}_2\text{CH}_2\text{OCH}_3)\text{OC}(\text{O})\text{C}(\text{CH}_3)_3$,

- 20  ; $-\text{CH}_2\text{OC}(\text{O})\text{C}_{10}\text{H}_{15}$, $-\text{CH}_2\text{OC}(\text{O})\text{C}(\text{CH}_3)_3$, $-\text{CH}(\text{CH}_2\text{OCH}_3)\text{OC}(\text{O})\text{C}(\text{CH}_3)_3$, $-\text{CH}(\text{CH}(\text{CH}_3)_2)\text{OC}(\text{O})\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OC}(\text{O})\text{C}_6\text{H}_{11}$, $-\text{CH}_2\text{OC}(\text{O})\text{C}_6\text{H}_5$, $-\text{CH}_2\text{OC}(\text{O})\text{C}_{10}\text{H}_{15}$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OC}(\text{O})\text{C}(\text{CH}_3)_3$ and $-\text{CH}_2\text{OC}(\text{O})\text{CH}_2\text{C}_6\text{H}_5$.

For prodrug purposes, the ester typically chosen is one heretofore used for antibiotic drugs, in particular the cyclic carbonates, double esters, or the phthalidyl, aryl or alkyl esters.

As noted, R_{6a}, R_{6c} and R_{6b} groups optionally are used to prevent side reactions with the protected group during synthetic procedures, so they function as protecting groups (PRT) during synthesis. For the most part the decision as to which groups to protect, when to do so, and the nature of the PRT will be dependent upon the chemistry of the reaction to be protected against (e.g., acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PRT groups do not need to be, and generally are not, the same if the compound is substituted with multiple PRT. In general, PRT will be used to protect carboxyl, hydroxyl or amino groups. The order of deprotection to yield free groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

A very large number of R_{6a} hydroxy protecting groups and R_{6c} amide-forming groups and corresponding chemical cleavage reactions are described in "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; "Protecting Groups" (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For R_{6a} carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for W₁ acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

In some embodiments the R_{6a} protected acidic group is an ester of the acidic group and R_{6a} is the residue of a hydroxyl-containing functionality. In other embodiments, an R_{6c} amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as

groups L1 or L2. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be understood that such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

5 Typical R_{6a} esters for protecting W₁ acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R³¹ or R³⁵), the table on page 105, and pages 21-23 (as R). Of
10 particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such as benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl, especially phenyl, ortho-ethoxyphenyl, or C₁-C₄ alkylestercarboxyphenyl (salicylate C₁-C₁₂ alkylesters).

15 The protected acidic groups W₁, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the W₁ acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are
20 administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

25 One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, e.g., the esters may be different or the same, or a mixed amidate and ester may be used.

30 Typical R_{6a} hydroxy protecting groups described in Greene (pages 14-118) include Ethers (Methyl); Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenylloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydrothiopyranyl, 1-Methoxycyclohexyl, 4-Methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-
35 Methoxytetrahydrothiopyranyl *S,S*-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 35, 1,4-Dioxan-2-yl, Tetrahydrofuranyl,

Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)); Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilyl ethyl, 2-(Phenylselenyl)ethyl, *t*-Butyl, Allyl, *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl); Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picolyl *N*-Oxido, Diphenylmethyl, *p,p'*-Dinitrobenzhydryl, 5-Dibenzosuberonyl, Triphenylmethyl, α -Naphthyl diphenylmethyl, *p*-methoxyphenyl diphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyl diphenylmethyl, 4,4',4''-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-Tris(levulinoyloxyphenyl)methyl, 4,4',4''-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-yl)methyl bis(4',4''-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl *S,S*-Dioxido); Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylhexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-Butylmethoxyphenylsilyl); Esters (Formate, Benzoylformate, Acetate, Chloroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate)); Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl, *p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate); Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-

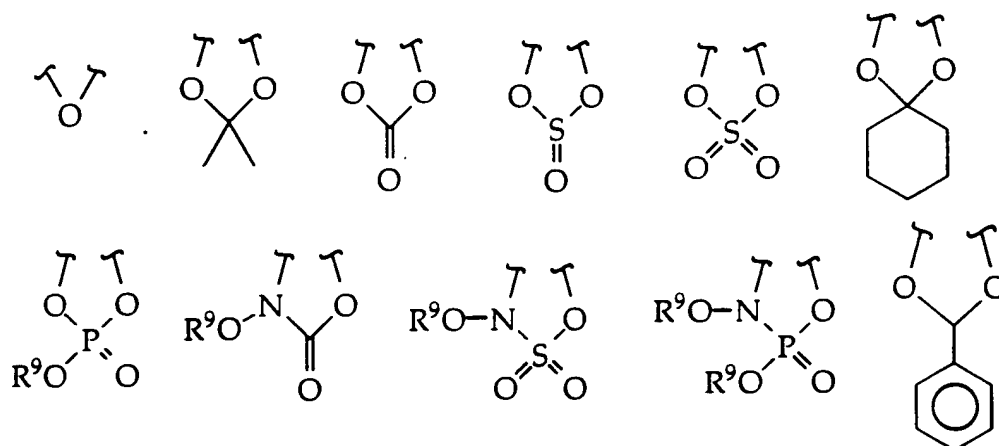
methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, Chorodiphenylacetate, Isobutyrate, Monosuccinoate, (*E*)-2-Methyl-2-butenolate (Tigloate), *o*-(Methoxycarbonyl)benzoate, *p*-poly-Benzoate, α -Naphthoate, 5 Nitrate, Alkyl *N,N,N',N'*-Tetramethylphosphorodiamidate, *N*-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzyisulfonate, Tosylate).

10 More typically, R_{6a} hydroxy protecting groups include substituted methyl ethers, substituted benzyl ethers, silyl ethers, and esters including sulfonic acid esters, still more typically, trialkylsilyl ethers, tosylates and acetates.

Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the R_{6a} protecting functionality) are described 15 in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-*t*-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, *p*-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4- 20 Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidene, 1,2-Dimethoxyethylidene, α -Methoxybenzylidene, 1-(*N,N*-Dimethylamino)ethylidene Derivative, α -(*N,N*-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl 25 Derivatives (Di-*t*-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropylidisiloxanylidene), and Tetra-*t*-butoxydisiloxane-1,3-diylidene), Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate and Phenyl Boronate.

More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ketals and aryl acetals.

Table B



wherein R^9 is C_1 - C_6 alkyl.

- 5 R_{6b} is H, a protecting group for amino or the residue of a carboxyl-containing compound, in particular H, $-C(O)R_4$, an amino acid, a polypeptide or a protecting group not $-C(O)R_4$, amino acid or polypeptide. Amide-forming R_{6b} are found for instance in group G1. When R_{6b} is an amino acid or polypeptide it has the structure $R_{15}NHCH(R_{16})C(O)-$, where R_{15} is H, an amino acid or polypeptide residue, or R_5 , and R_{16} is defined below.

- 10 R_{16} is lower alkyl or lower alkyl (C_1 - C_6) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, C_6 - C_7 aryl, guanidiny, imidazolyl, indolyl, sulfhydryl, sulfoxide, and/or alkylphosphate. R_{10} also is taken together with the amino acid α N to form a proline residue ($R_{10} = -CH_2)_3$).
- 15 However, R_{10} is generally the side group of a naturally-occurring amino acid such as H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH(CH_3)_2$, $-CHCH_3-CH_2-CH_3$, $-CH_2-C_6H_5$, $-CH_2CH_2-S-CH_3$, $-CH_2OH$, $-CH(OH)-CH_3$, $-CH_2-SH$, $-CH_2-C_6H_4OH$, $-CH_2-CO-NH_2$, $-CH_2-CH_2-CO-NH_2$, $-CH_2-COOH$, $-CH_2-CH_2-COOH$, $-(CH_2)_4-NH_2$ and $-(CH_2)_3-NH-C(NH_2)-NH_2$. R_{10} also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

- 20 R_{6b} are residues of carboxylic acids for the most part, but any of the typical amino protecting groups described by Greene at pages 315-385 are useful. They include Carbamates (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-buthyl-[9-(10,10-dioxo-10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl); Substituted Ethyl (2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-

dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidiny, alkylidithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl); Groups With Assisted Cleavage (2-methylthioethyl, 2-methylsulfonyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-choro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl); Groups Capable of Photolytic Cleavage (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl);

15 Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothiocarbonyl); Miscellaneous Carbamates (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-

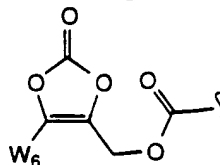
20 dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p'*-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl,

25 phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl); Amides (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichoroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-benzoylphenylalanyl, *N*-benzoyl, *N*-*p*-phenylbenzoyl); Amides With Assisted Cleavage (*N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxycetyl, *N*-acetoacetyl, (*N'*-dithiobenzoyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-

35 nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one); Cyclic Imide

- Derivatives (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl);
- 5 *N*-Alkyl and *N*-Aryl Amines (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-
- 10 fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolyllamine *N*'-oxide), Imine Derivatives (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*-(*N*',*N*'-dimethylaminomethylene, *N*,*N*'-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-
- 15 hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene); Enamine Derivatives (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)); *N*-Metal Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate); *N*-N Derivatives (*N*-nitro, *N*-nitroso, *N*-oxide); *N*-P Derivatives (*N*-
- 20 diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl); *N*-Si Derivatives; *N*-S Derivatives; *N*-Sulfonyl Derivatives (*N*-benzenesulfonyl, *N*-*o*-nitrobenzenesulfonyl, *N*-2,4-dinitrobenzenesulfonyl, *N*-pentachlorobenzenesulfonyl, *N*-2-nitro-4-
- 25 methoxybenzenesulfonyl, *N*-triphenylmethylsulfonyl, *N*-3-nitropyridinesulfonyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6,-tetramethyl-4-
- 30 methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*- β -trimethylsilyl ethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-
- 35 trifluoromethylsulfonyl, *N*-phenacylsulfonyl).

More typically, protected amino groups include carbamates and amides, still more typically, -NHC(O)R_1 or $\text{-N=CR}_1\text{N(R}_1)_2$. Another protecting group, also usefull as a prodrug at the G₁ site, particularly for amino or $\text{-NH(R}_5\text{)}$, is:



5

see for example Alexander, J.; et al.; *J. Med. Chem.* 1996, 39, 480-486.

R_{6c} is H or the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, $\text{-NHSO}_2\text{R}_4$, NHC(O)R_4 , $\text{-N(R}_4)_2$, NH_2 or $\text{-NH(R}_4\text{)(H)}$, whereby for example the carboxyl or
 10 phosphonic acid groups of W_1 are reacted with the amine to form an amide, as in -C(O)R_{6c} , $\text{-P(O)(R}_{6c})_2$ or $\text{-P(O)(OH)(R}_{6c})$. In general, R_{6c} has the structure $\text{R}_{17}\text{C(O)CH(R}_{16})\text{NH-}$, where R_{17} is OH, OR_{6a} , OR_5 , an amino acid or a polypeptide residue.

Amino acids are low molecular weight compounds, on the order of less
 15 than about 1,000 MW, that contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, i.e., can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, i.e. compounds characterized by one amino or imino nitrogen atom separated
 20 from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono-or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not
 25 contain a sulphydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine,
 30 valine, leucine, isoleucine, serine, threonine; cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline.

When R_{6b} and R_{6c} are single amino acid residues or polypeptides they usually are substituted at R_3 , W_6 , W_1 and/or W_2 , but typically only W_1 or

W₂. These conjugates are produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example) and W₂. Similarly, conjugates are formed between W₁ and an amino group of an amino acid or polypeptide. Generally, only one of any site in the parental molecule is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of W₁ is amidated with an amino acid. In general, the α -amino or α -carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the parental functionalities, i.e., carboxyl or amino groups in the amino acid side chains generally are not used to form the amide bonds with the parental compound (although these groups may need to be protected during synthesis of the conjugates as described further below).

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, e.g. by R_{6a}, esterified with R₅ or amidated with R_{6c}. Similarly, the amino side chains R₁₆ optionally will be blocked with R_{6b} or substituted with R₅.

Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable in vivo or in vitro under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The esters or amino acid or polypeptide amidates also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are useful. On the other hand, L isomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more

efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R_{6b} and R_{6c} include the following:

5 Glycine;

Aminopolycarboxylic acids, e.g., aspartic acid, β -hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β -methylaspartic acid, β -methylglutamic acid, β,β -dimethylaspartic acid, γ -hydroxyglutamic acid, β,γ -dihydroxyglutamic acid, β -phenylglutamic acid, γ -methyleneglutamic acid, 3-
10 aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyric acid, ornithine, citrulline, homoarginine,
15 homocitrulline, hydroxylysine, allohydroxylysine and diaminobutyric acid;

Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α,α' -diaminosuccinic acid, α,α' -diaminoglutaric acid, α,α' -diaminoadipic acid, α,α' -diaminopimelic acid, α,α' -diamino- β -hydroxypimelic acid, α,α' -diaminosuberic acid, α,α' -
20 diaminoazelaic acid, and α,α' -diaminosebacic acid;

Imino acids such as proline, hydroxyproline, allohydroxyproline, γ -methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C₁ - C₈ branched or normal) amino acid
25 such as alanine, valine, leucine, allylglycine, butyric acid, norvaline, norleucine, heptyline, α -methylserine, α -amino- α -methyl- γ -hydroxyvaleric acid, α -amino- α -methyl- δ -hydroxyvaleric acid, α -amino- α -methyl- ϵ -hydroxycaproic acid, isovaline, α -methylglutamic acid, α -aminoisobutyric acid, α -aminodiethylacetic acid, α -aminodiisopropylacetic acid, α -aminodi-n-propylacetic acid, α -aminodiisobutylacetic acid, α -aminodi-n-butylacetic acid,
30 α -aminoethylisopropylacetic acid, α -amino-n-propylacetic acid, α -aminodiisoamylacetic acid, α -methylaspartic acid, α -methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloseucine, tert-leucine, β -methyltryptophan and α -amino- β -ethyl- β -phenylpropionic acid;

35 β -phenylserinyl;

Aliphatic α -amino- β -hydroxy acids such as serine, β -hydroxyisoleucine, β -

hydroxynorleucine, β -hydroxynorvaline, and α -amino- β -hydroxystearic acid;

α -Amino, α -, γ -, δ - or ϵ -hydroxy acids such as homoserine, γ -hydroxynorvaline, δ -hydroxynorvaline and epsilon-hydroxynorleucine residues; canavine and canaline; γ -hydroxyornithine;

- 5 2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α -Amino- β -thiols such as penicillamine, β -thiolnorvaline or β -thiolbutyrine;

Other sulfur containing amino acid residues including cysteine;

- 10 homocystine, β -phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α amino acids such as the phenyl- or cyclohexylamino acids α -aminophenylacetic acid, α -aminocyclohexylacetic acid and α -amino- β -cyclohexylpropionic acid;

- 15 phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dicloro, o-, m- or p-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthyl-
20 alanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α -Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-
25 benzylvaline; and

α -Hydroxy and substituted α -hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

- Polypeptides are polymers of amino acids in which a carboxyl group of one amino acid monomer is bonded to an amino or imino group of the next
30 amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial proteins. They include enzymes (e.g., hydrogen peroxidase) as well
35 as immunogens such as KLH, or antibodies or proteins of any type against

which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amidates are useful as immunogens in raising antibodies against either the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may not need to be immunogenic in an animal typically used to raise antibodies, e.g., rabbit, mouse, horse, or rat, but the final product conjugate should be immunogenic in at least one of such animals. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, e.g. a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases. Carboxypeptidases digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α -amino group to the phosphorus or carbon atoms of the compounds herein. In embodiments where W₁ is phosphonate it is expected that this peptide will be cleaved by the appropriate peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH,

DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN, TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY and VV.

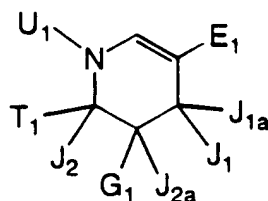
Tripeptide residues are also useful as R_{6b} or R_{6c}. When W₁ is phosphonate, the sequence -X₄-pro-X₅- (where X₄ is any amino acid residue and X₅ is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to yield X₄ with a free carboxyl, which in turn is expected to autocatalytically cleave the phosphonoamidate bond.

The carboxy group of X₅ optionally is esterified with benzyl.

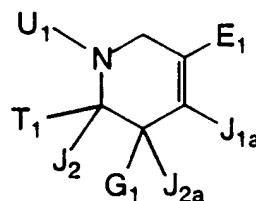
Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α -amino group are transport substrates for the peptide transporter found in brush border membrane of intestinal mucosal cells (Bai, J.P.F., "Pharm Res." 9:969-978 (1992)). Transport competent peptides can thus be used to enhance bioavailability of the amidate compounds. Di- or tripeptides having one or more amino acids in the D configuration are also compatible with peptide transport and can be utilized in the amidate compounds of this invention. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the

brush border such as aminopeptidase N (EC 3.4.11.2). In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor substrates for aminopeptidase A (EC 3.4.11.7), di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids (leu, tyr, phe, val, trp) are poor substrates for endopeptidase 24.11 (EC 3.4.24.11), and peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P (EC 3.4.17). Similar considerations can also be applied to the selection of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly cleaved polypeptide amidates are immunogens or are useful for bonding to proteins in order to prepare immunogens.

Another embodiment of the invention relates to compositions of the formula (VII) or (VIII):



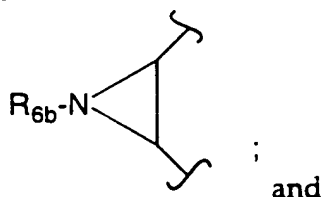
(VII)



(VIII)

wherein E₁, G₁, T₁, U₁, J₁, J_{1a}, J₂ and J_{2a} are as defined above except:

T₁ is -NR₁W₃, a heterocycle, or is taken together with G₁ to form a group having the structure



X₁ is a bond, -O-, -N(H)-, -N(R₅)-, -S-, -SO-, or -SO₂-; and provided, however, that compounds are excluded wherein U₁ is H or -CH₂CH(OH)CH₂(OH);

and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

Each of the typical or ordinary embodiments of formula (I)-(VI) detailed above are also typical embodiments of formula (VII) and (VIII).

The synthesis of a number of compounds of the formula (VII) and (VIII) wherein U₁ is H or -CH₂CH(OH)CH₂(OH) are provided in Nishimura, Y.; et al.; I. Antibiotics, 1993, 46(2), 300; 46(12), 1883; and Nat. Prod. Lett. 1992, 1(1), 39. Attachment of U₁ groups of the present invention proceed as described

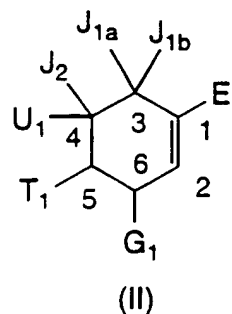
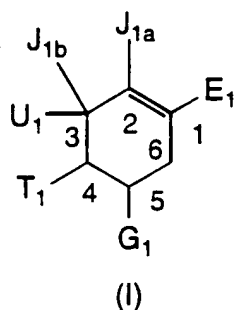
5 therein.

Stereoisomers

The compounds of the invention are enriched or resolved optical isomers at any or all asymmetric atoms. For example, the chiral centers
10 apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual,
15 substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate
20 stereoisomer of the desired starting material.

Exemplary stereochemistry of the compounds of this invention is set forth below in Table C.

Table C



5 Formula (I)

E ₁	J _{1a}	J _{1b}	U ₁	T ₁	G ₁
-	-	α	β	α	α
-	-	β	α	α	α
-	-	α	β	β	α
-	-	α	β	α	β
		β	α	β	α
		β	α	α	β
		α	β	β	β
		β	α	β	β

Formula (I)

E ₁	J _{1a}	J _{1b}	J ₂	U ₁	T ₁	G ₁
-	α	β	α	β	α	α
-	β	α	α	β	α	α
-	α	β	β	α	α	α
-	α	β	α	β	β	α
-	α	β	α	β	α	β
-	β	α	β	α	α	α
-	β	α	α	β	β	α
-	β	α	α	β	α	β
-	α	β	β	α	β	α
-	α	β	β	α	α	β
-	α	β	α	β	β	β
-	β	α	β	α	β	α
-	β	α	β	β	α	β
-	β	α	α	β	β	β
-	α	β	β	α	β	β
-	β	α	β	α	β	β

10

The compounds of the invention can also exist as tautomeric isomers in certain cases. For example, ene-amine tautomers can exist for imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Exemplary Enumerated Compounds.

- By way of example and not limitation, embodiment compounds are named below in tabular format (Table 6). Generally, each compound is depicted as a substituted nucleus in which the nucleus is designated by capital letter and each substituent is designated in order by lower case letter or number. Tables 1a and 1b are a schedule of nuclei which differ principally by the position of ring unsaturation and the nature of ring substituents. Each nucleus is given a alphabetical designation from Tables 1a and 1b, and this designation appears first in each compound name. Similarly, Tables 2a-av, 3a-b, 4a-c, and 5a-d list the selected Q₁, Q₂, Q₃ and Q₄ substituents, again by letter or number designation. Accordingly, each named compound will be depicted by a capital letter designating the nucleus from Table 1a-1b, followed by a number designating the Q₁ substituent, a lower case letter designating the Q₂ substituent, a number designating the Q₃ substituent, and a lower case letter or letters designating the Q₄ substituent. Thus, structure 8, scheme 1, is represented by A.49.a.4.i. Q₁-Q₄, it should be understood, do not represent groups or atoms but are simply connectivity designations.

Table 1a

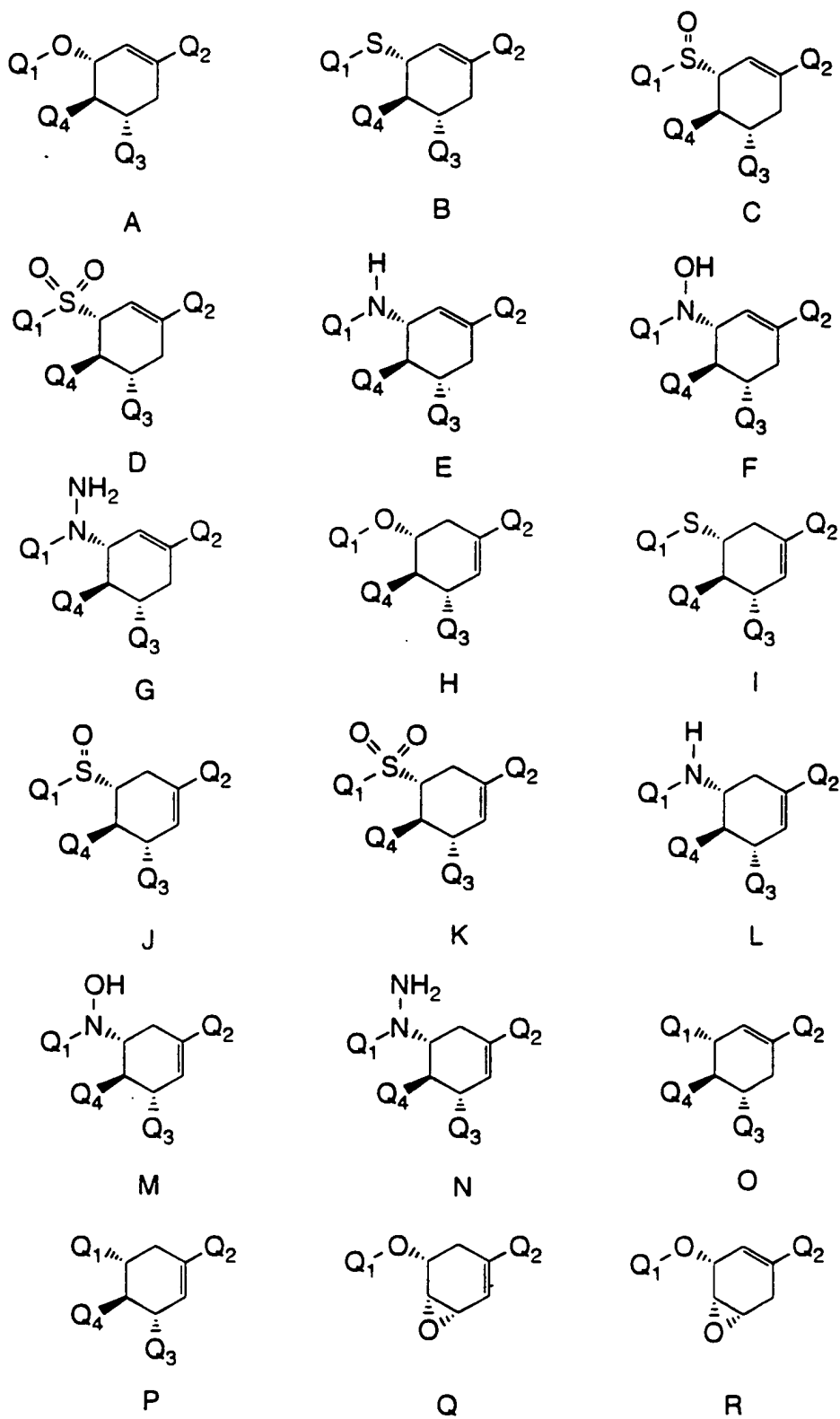
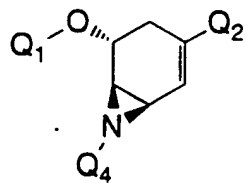
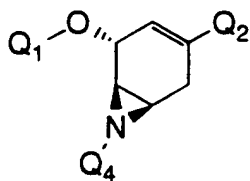


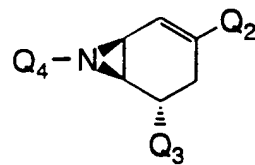
Table 1b



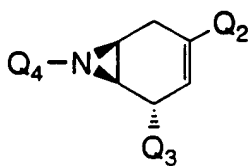
S



T



U



V

Table 2a

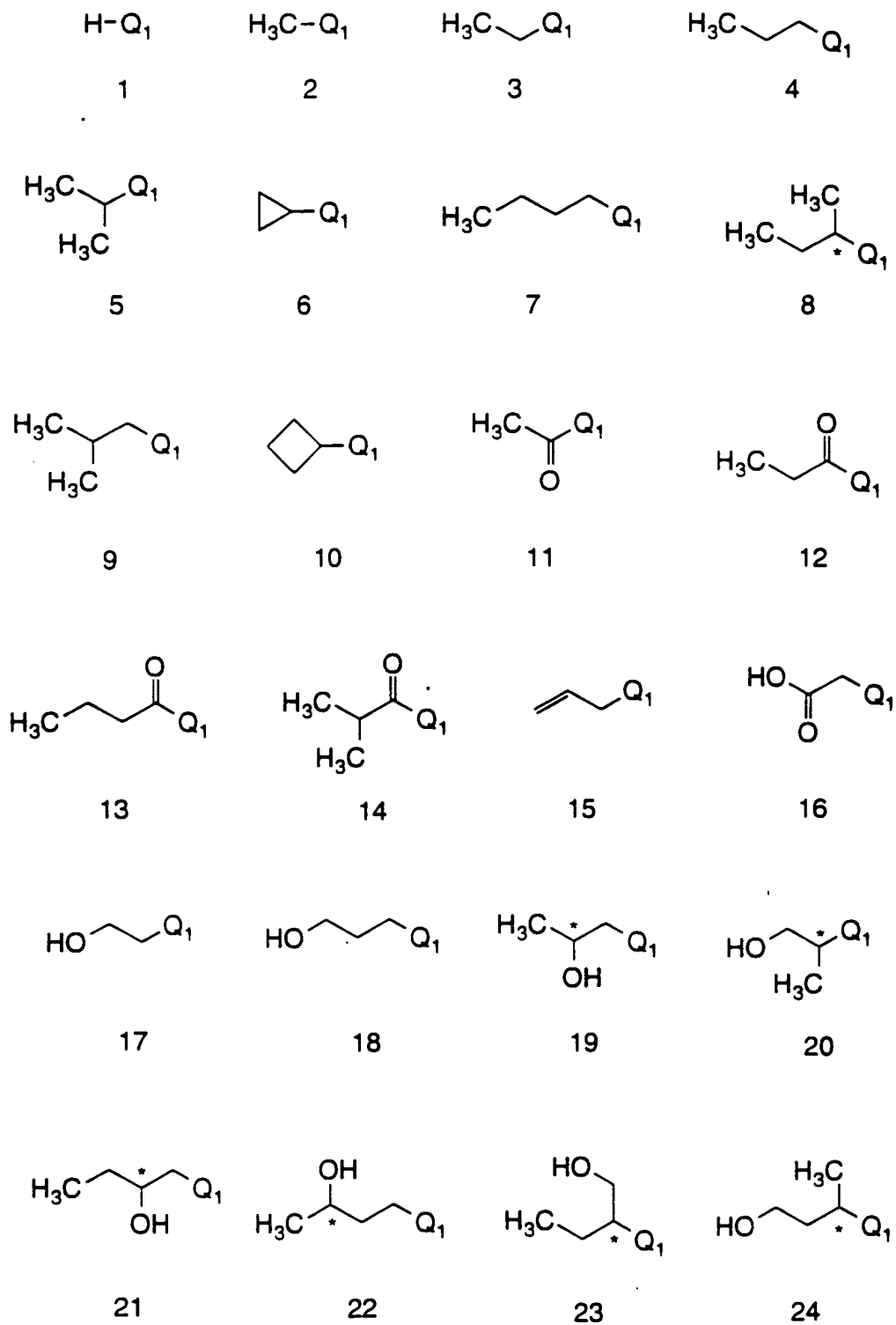


Table 2b

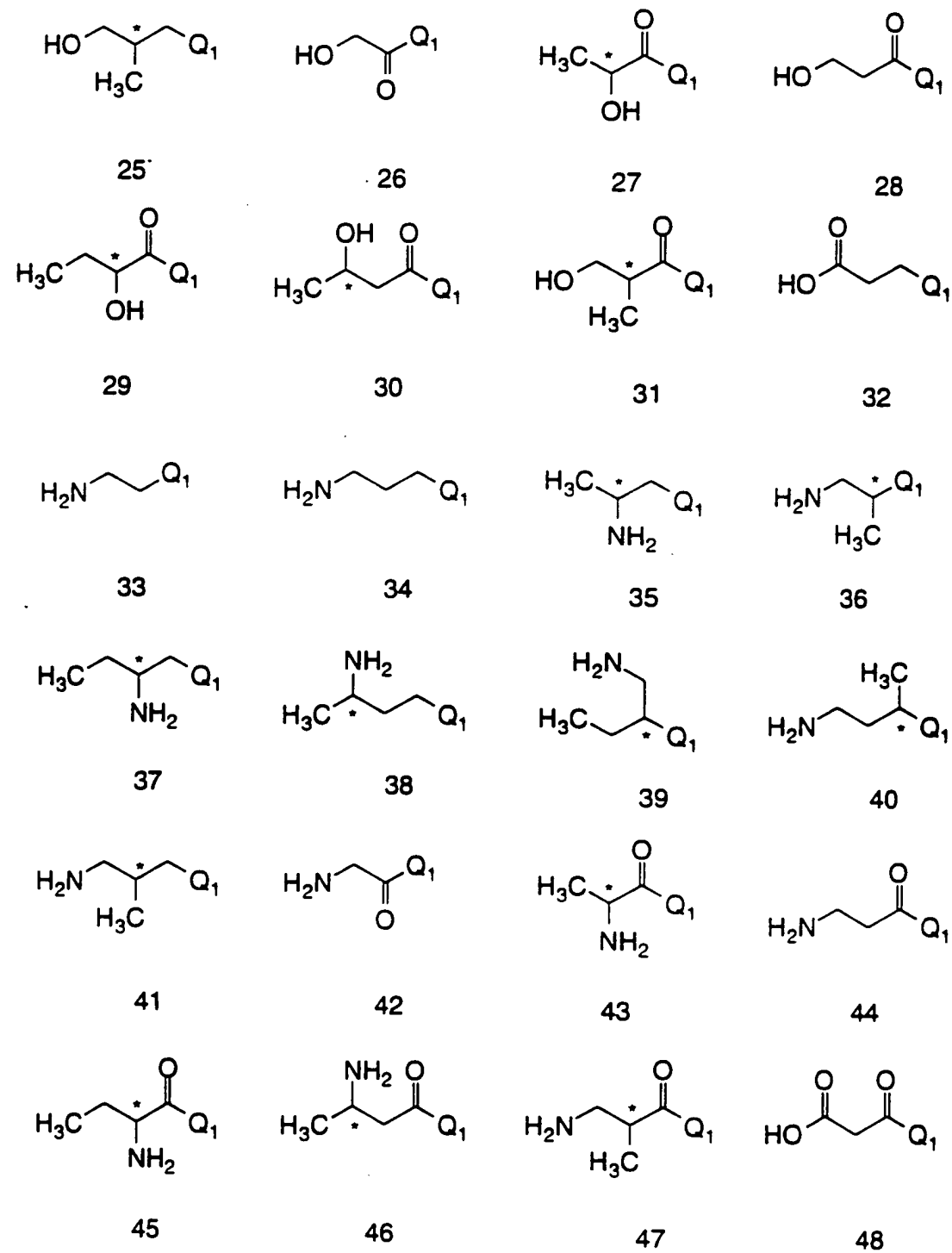
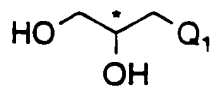
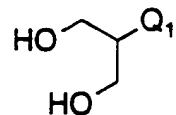


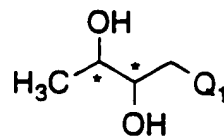
Table 2c



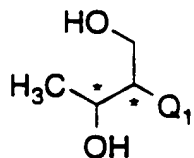
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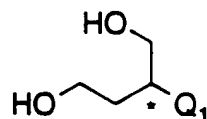
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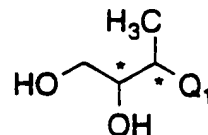
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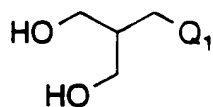
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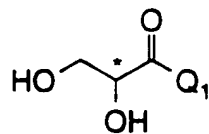
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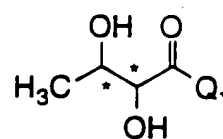
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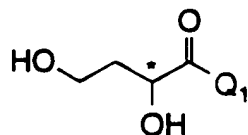
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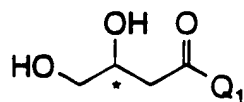
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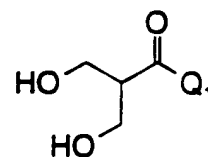
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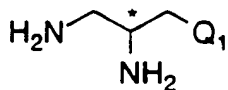
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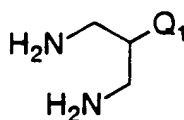
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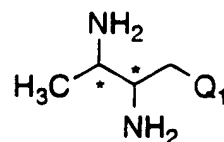
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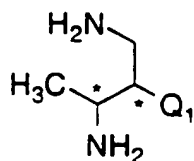
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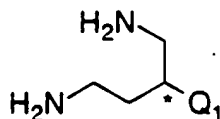
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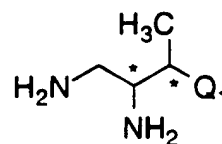
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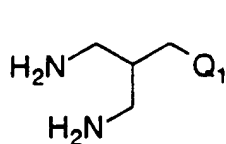


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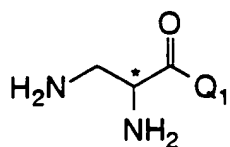


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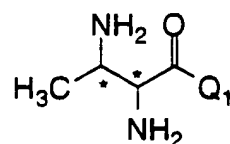
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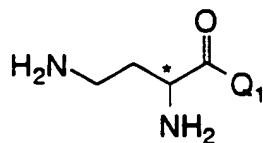
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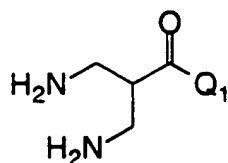
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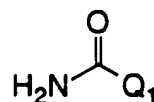
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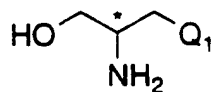
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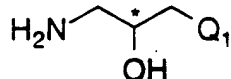
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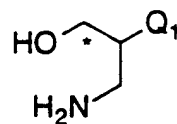
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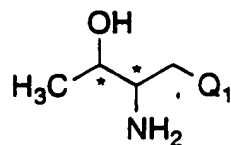
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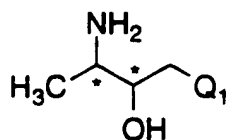
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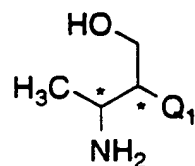
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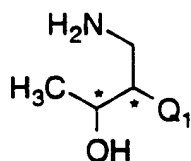
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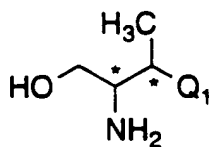
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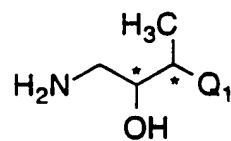
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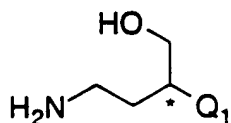
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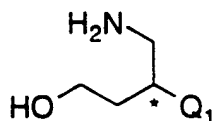
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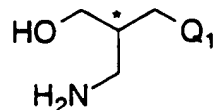
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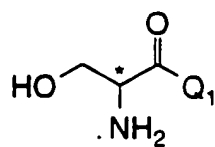


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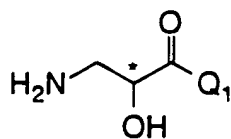


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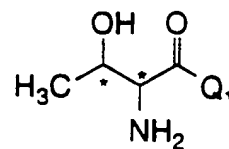
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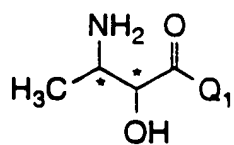
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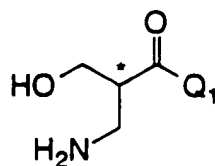
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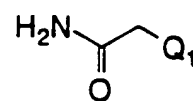
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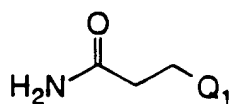
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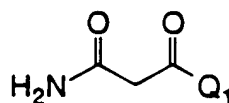
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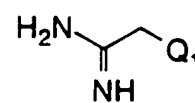
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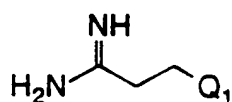
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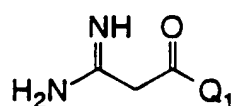
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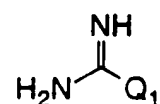
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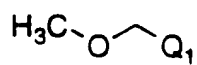
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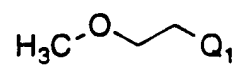
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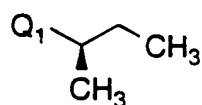
96



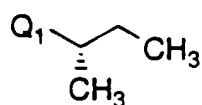
97



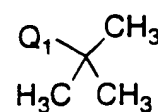
98



100

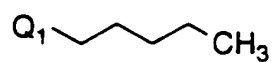


101

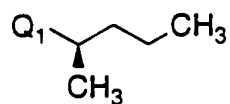


102

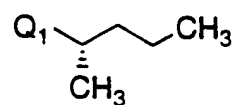
Table 2f



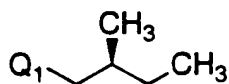
103



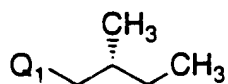
104



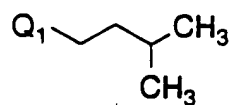
105



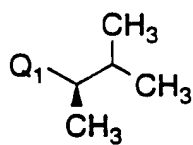
106



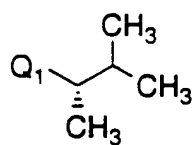
107



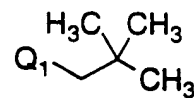
108



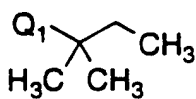
109



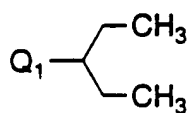
110



111



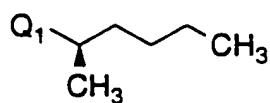
112



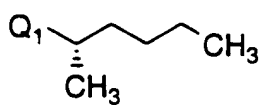
113



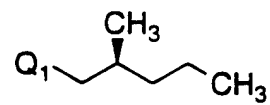
114



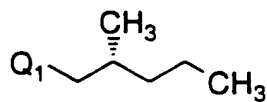
115



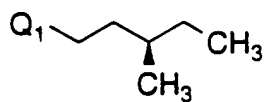
116



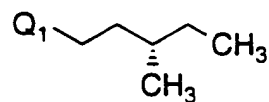
117



118

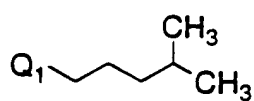


119

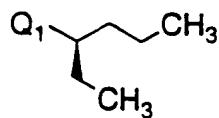


120

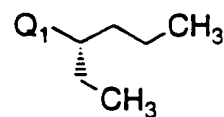
Table 2g



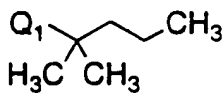
121



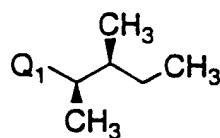
122



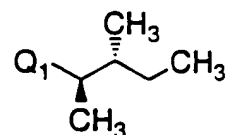
123



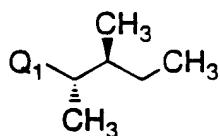
124



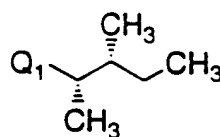
125



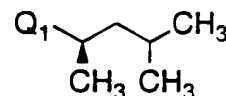
126



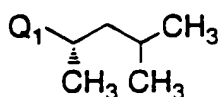
127



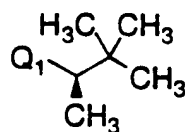
128



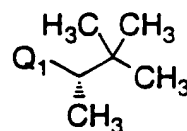
129



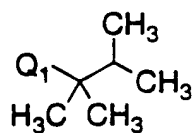
130



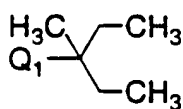
131



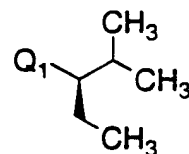
132



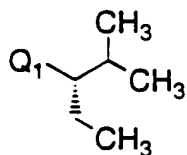
133



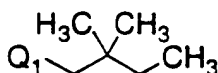
134



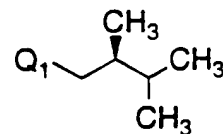
135



136

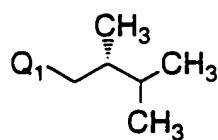


137

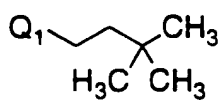


138

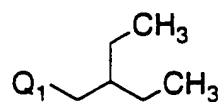
Table 2h



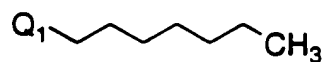
139



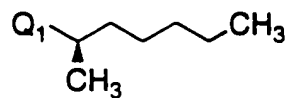
140



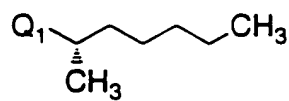
141



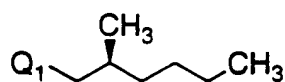
142



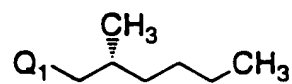
143



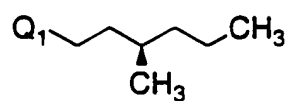
144



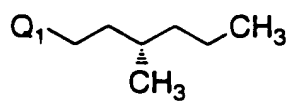
145



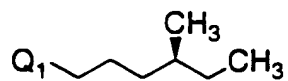
146



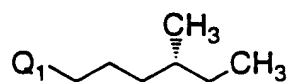
147



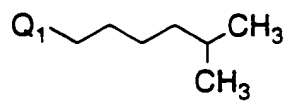
148



149

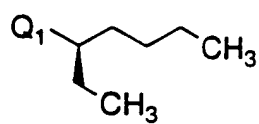


150

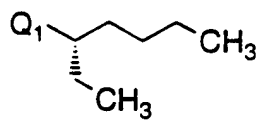


151

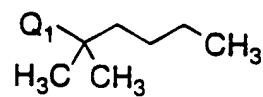
Table 2i



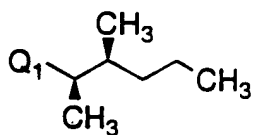
152



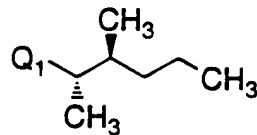
153



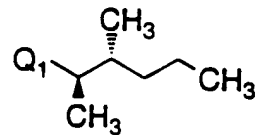
154



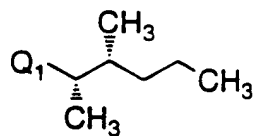
155



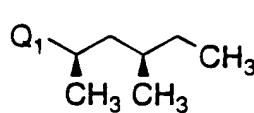
156



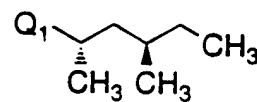
157



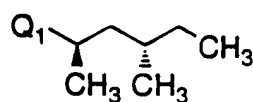
158



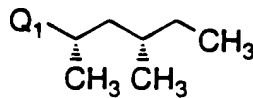
159



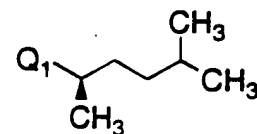
160



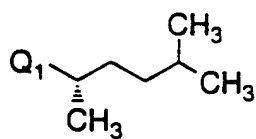
161



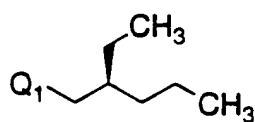
162



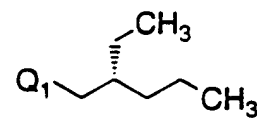
163



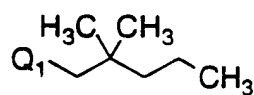
164



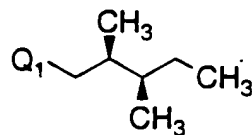
165



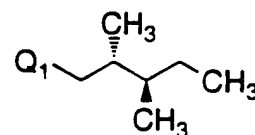
166



167

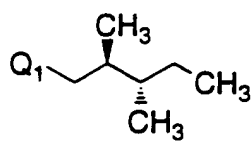


168

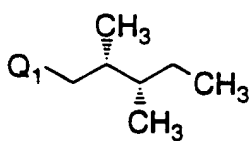


169

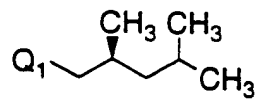
Table 2j



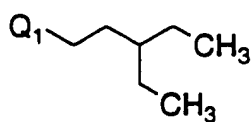
170



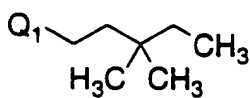
171



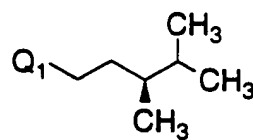
172



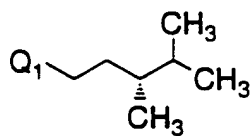
173



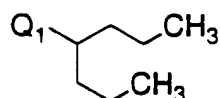
174



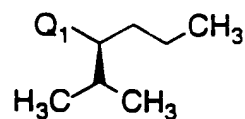
175



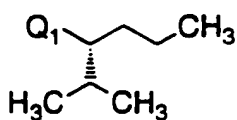
176



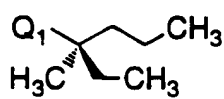
177



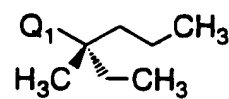
178



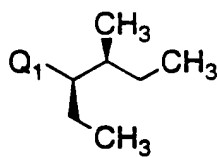
179



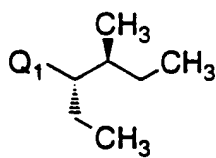
180



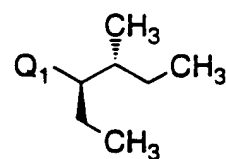
181



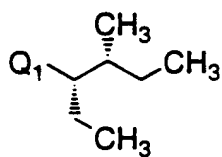
182



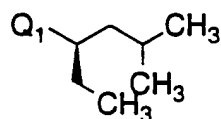
183



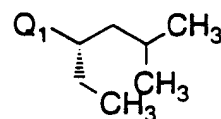
184



185

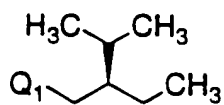


186

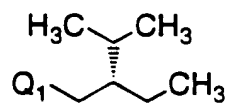


187

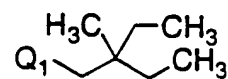
Table 2k



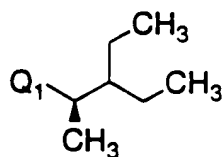
188



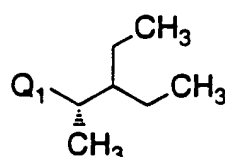
189



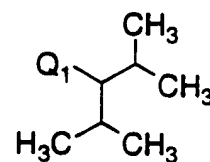
190



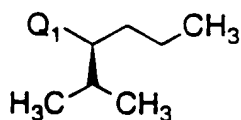
191



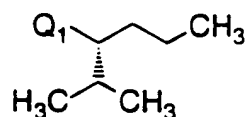
192



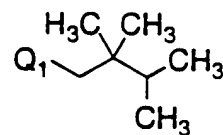
193



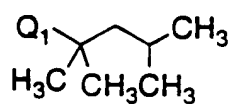
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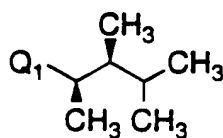
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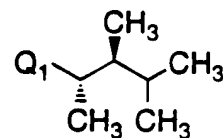
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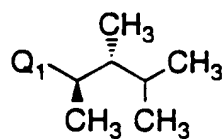
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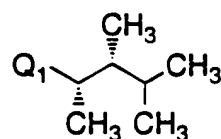
198



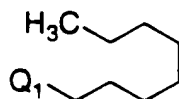
199



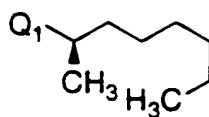
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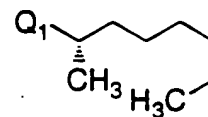
201



202

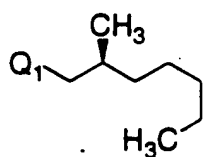


203

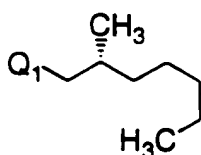


204

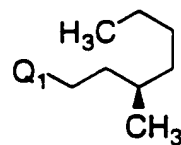
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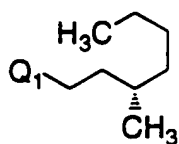
205



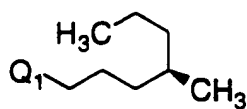
206



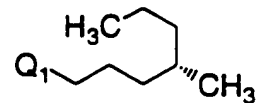
207



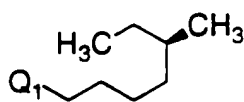
208



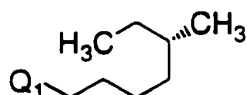
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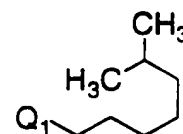
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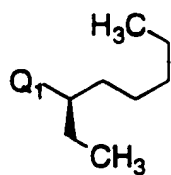
211



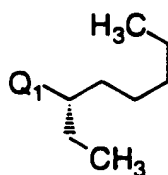
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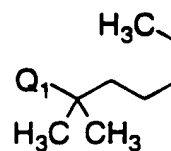
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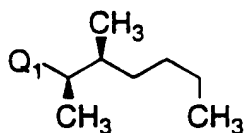
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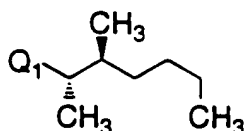
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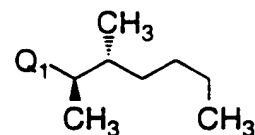
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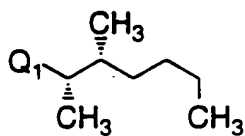
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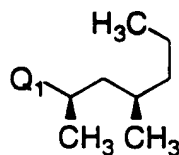
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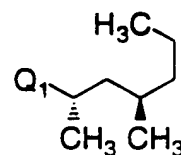
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220

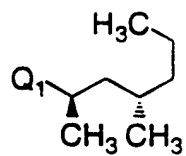


221

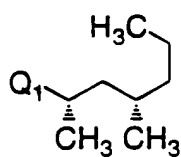


222

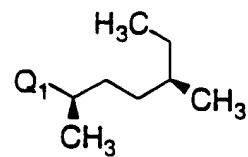
Table 2m



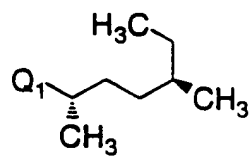
223



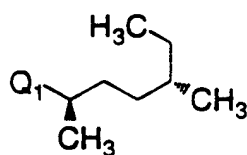
224



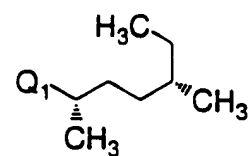
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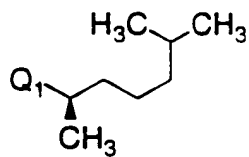
226



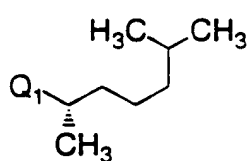
227



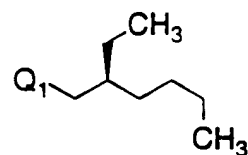
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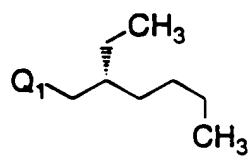
229



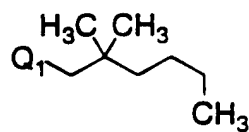
230



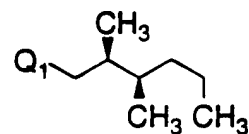
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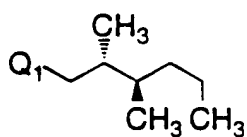
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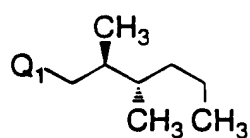
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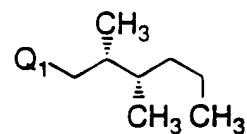
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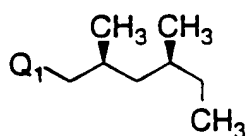
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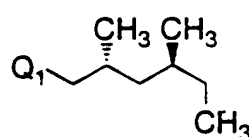
236



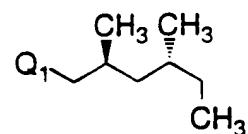
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238

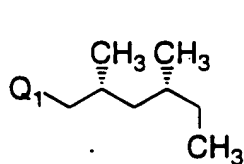


239

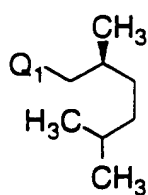


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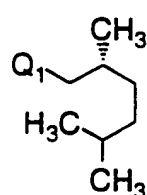
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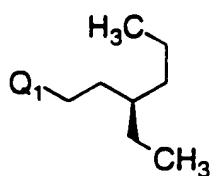
241



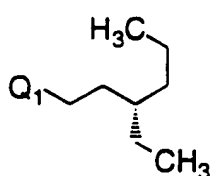
242



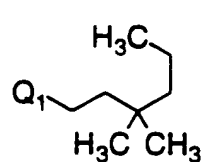
243



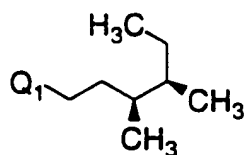
244



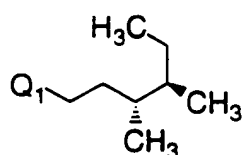
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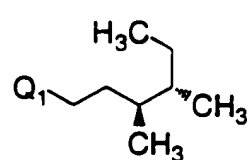
246



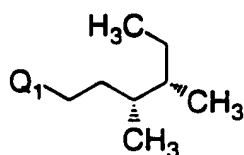
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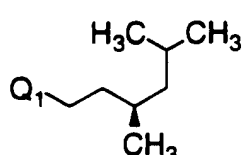
248



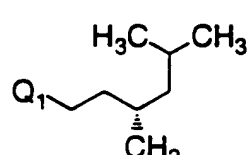
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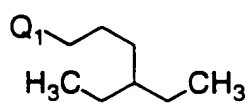
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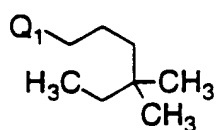
251



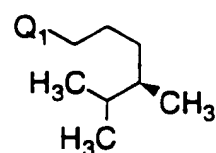
252



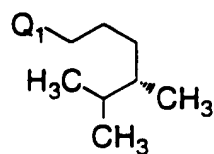
253



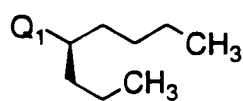
254



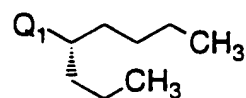
255



256

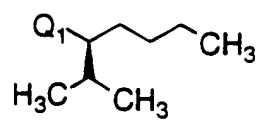


257

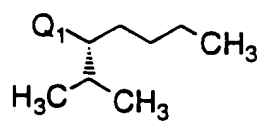


258

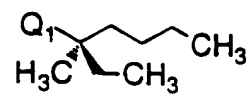
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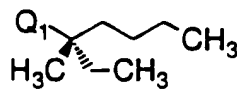
259



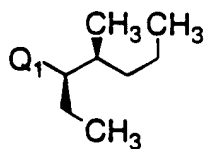
260



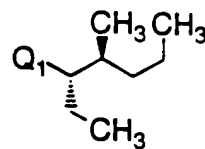
261



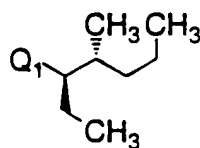
262



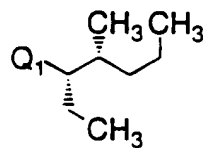
263



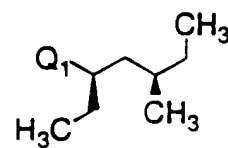
264



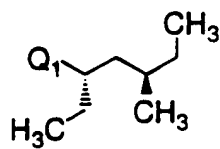
265



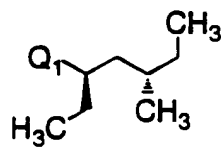
266



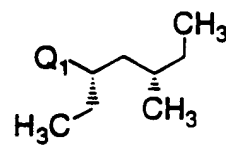
267



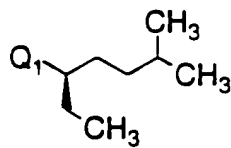
268



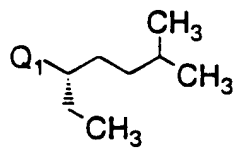
269



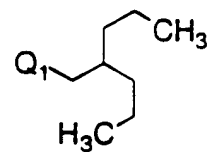
270



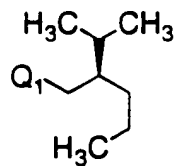
271



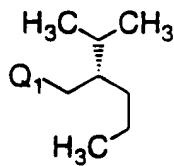
272



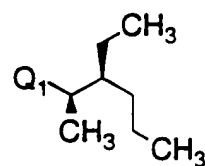
273



274

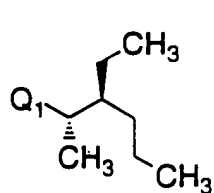


275

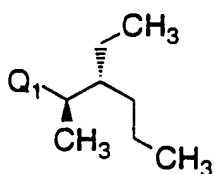


276

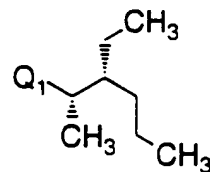
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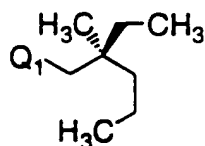
277



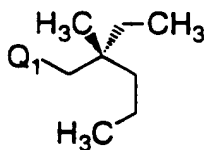
278



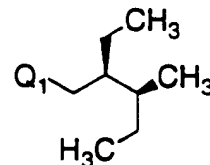
279



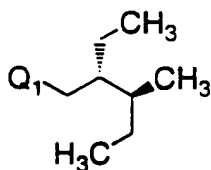
280



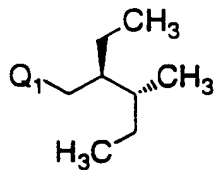
281



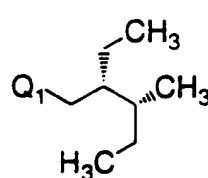
282



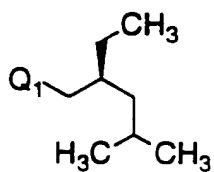
283



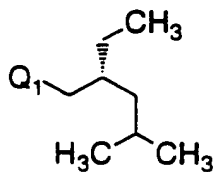
284



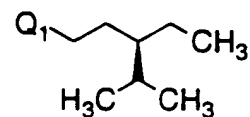
285



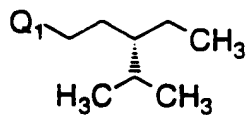
286



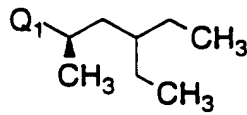
287



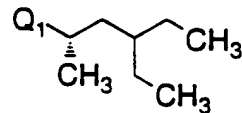
288



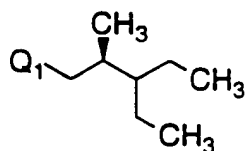
289



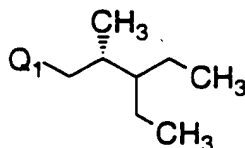
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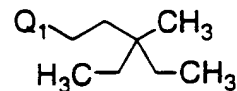
291



292

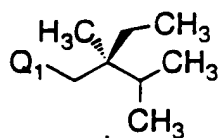


293

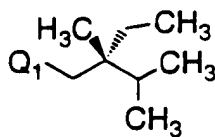


294

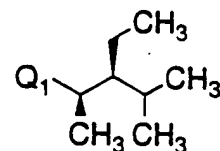
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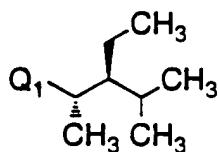
295



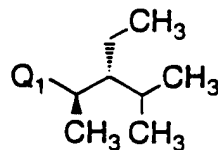
296



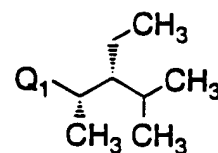
297



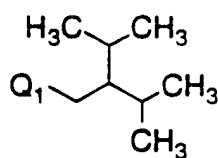
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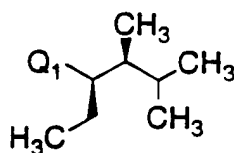
299



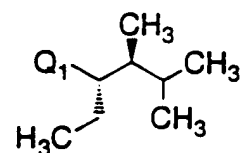
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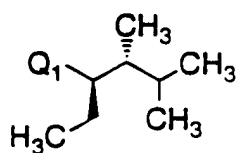
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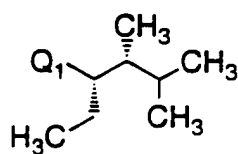
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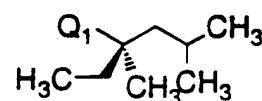
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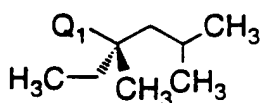
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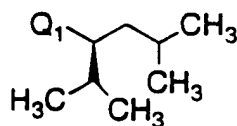
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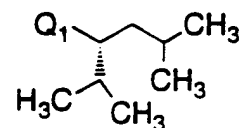
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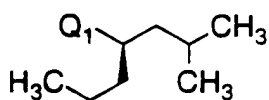
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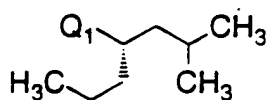
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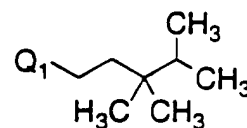
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310

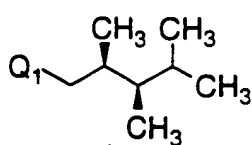


311

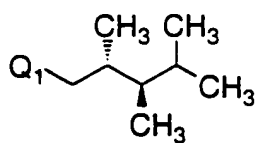


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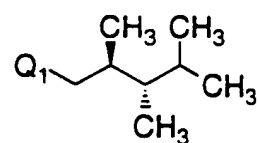
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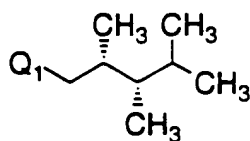
313



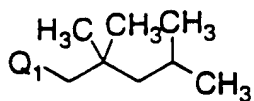
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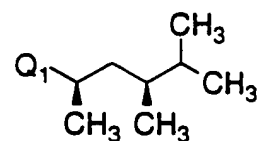
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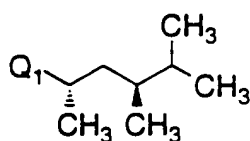
316



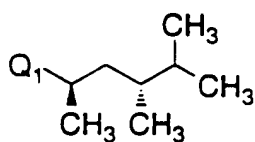
317



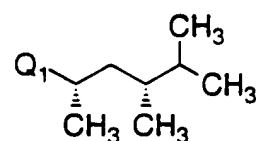
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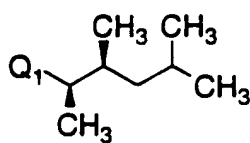
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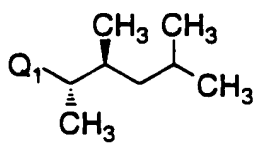
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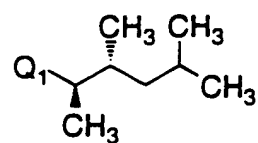
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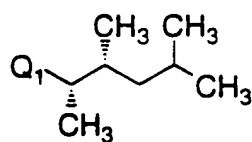
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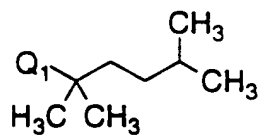
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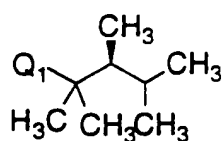
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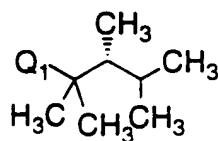
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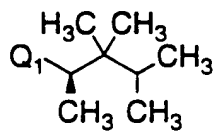
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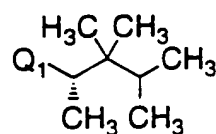
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328

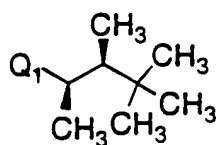


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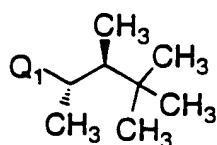


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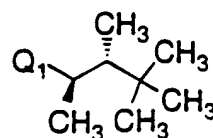
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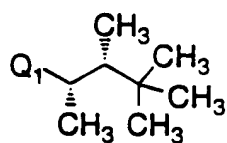
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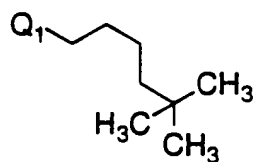
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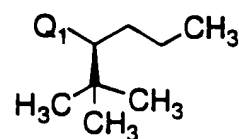
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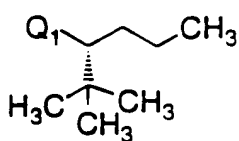
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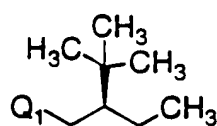
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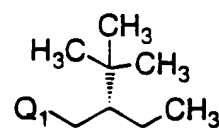
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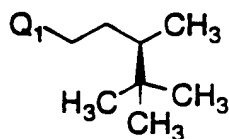
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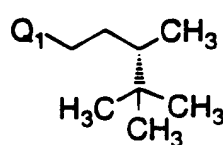
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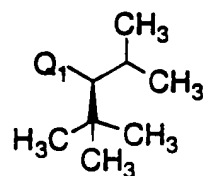
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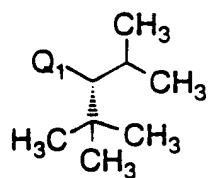
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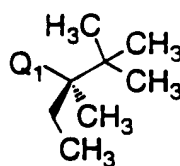
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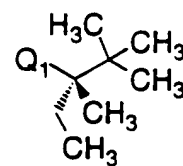
342



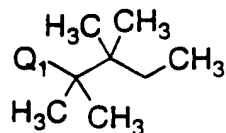
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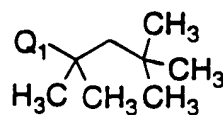
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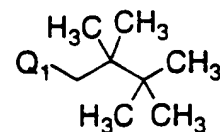
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346

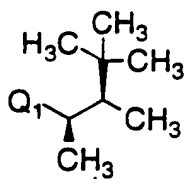


347

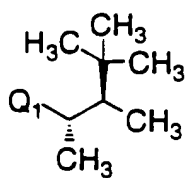


348

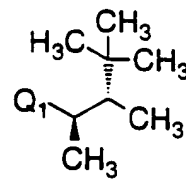
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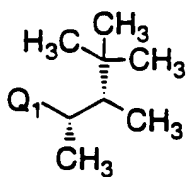
349



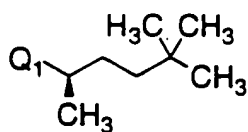
350



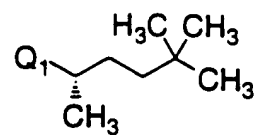
351



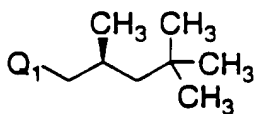
352



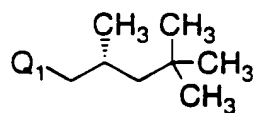
353



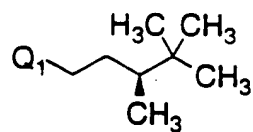
354



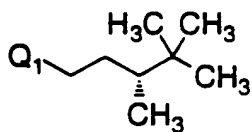
355



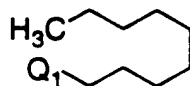
356



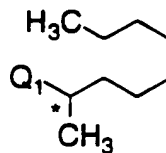
357



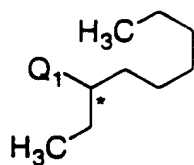
358



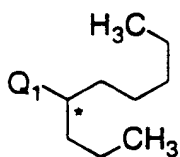
359



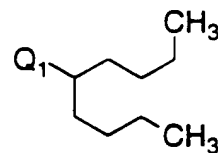
360



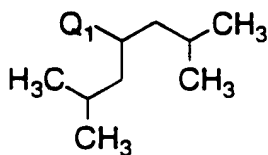
361



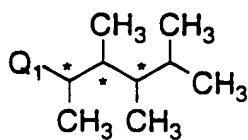
362



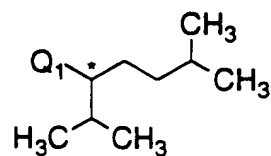
363



364

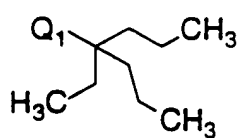


365

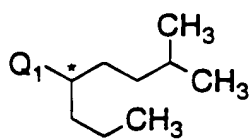


366

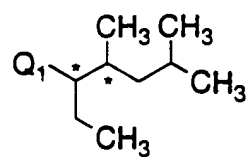
Table 2u



367



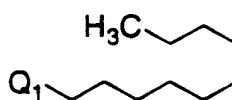
368



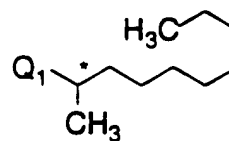
369



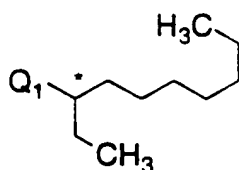
370



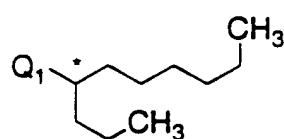
371



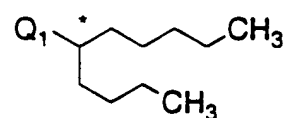
372



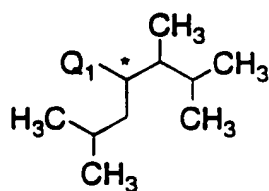
373



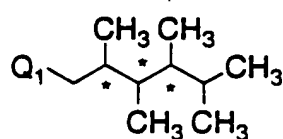
374



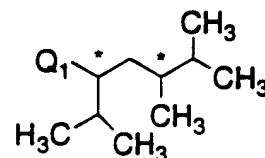
375



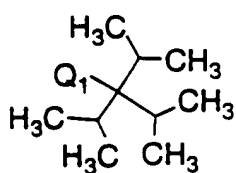
376



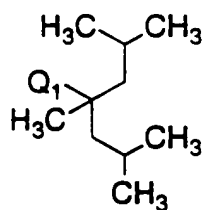
377



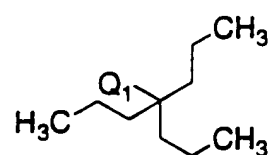
378



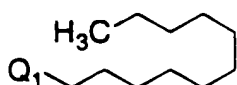
379



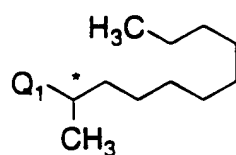
380



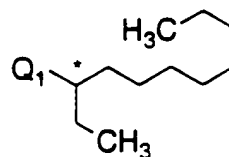
381



382

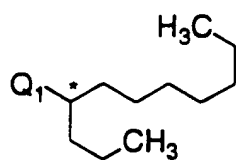


383

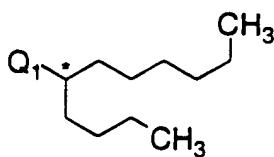


384

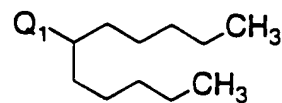
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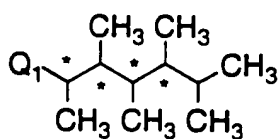
385



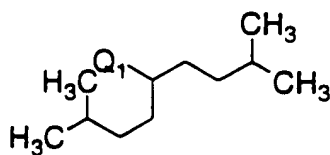
386



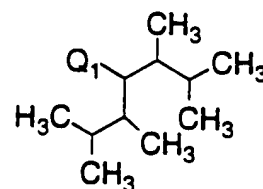
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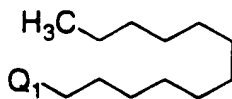
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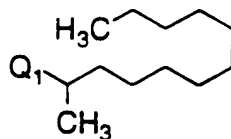
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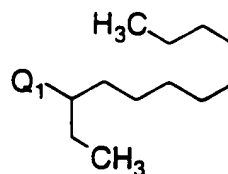
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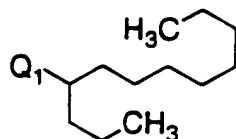
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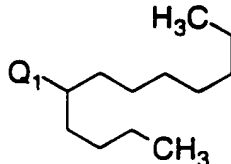
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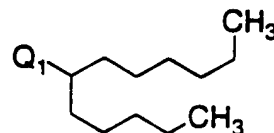
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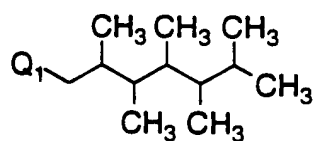
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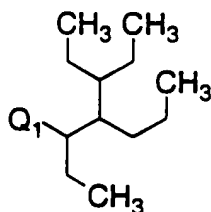
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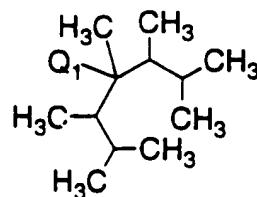
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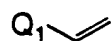


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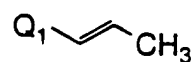


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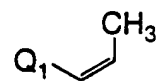
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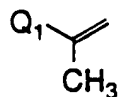
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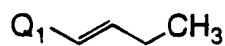
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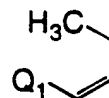
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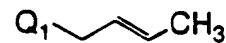
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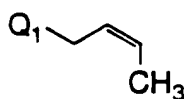
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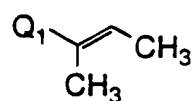
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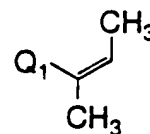
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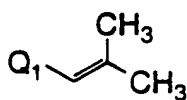
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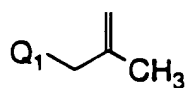
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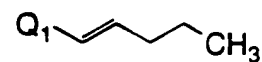
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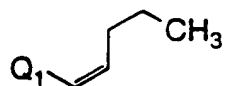
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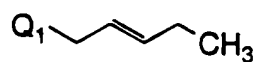
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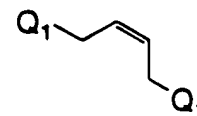
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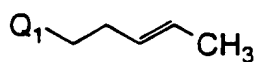
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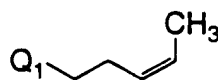
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416



417

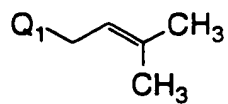


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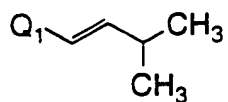


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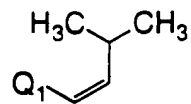
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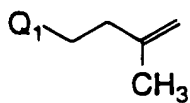
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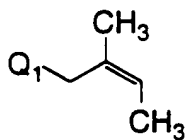
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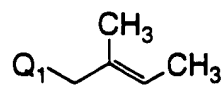
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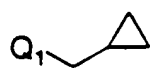
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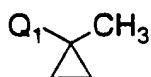
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425



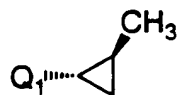
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427



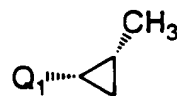
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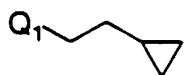
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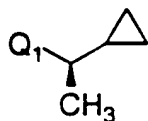
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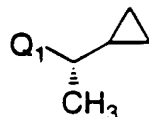
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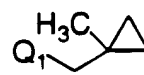
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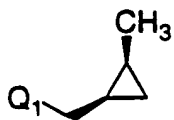
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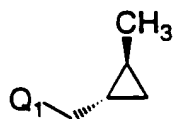
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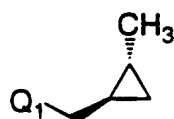
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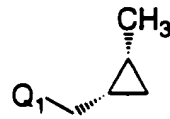
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437



438



439

Table 2y

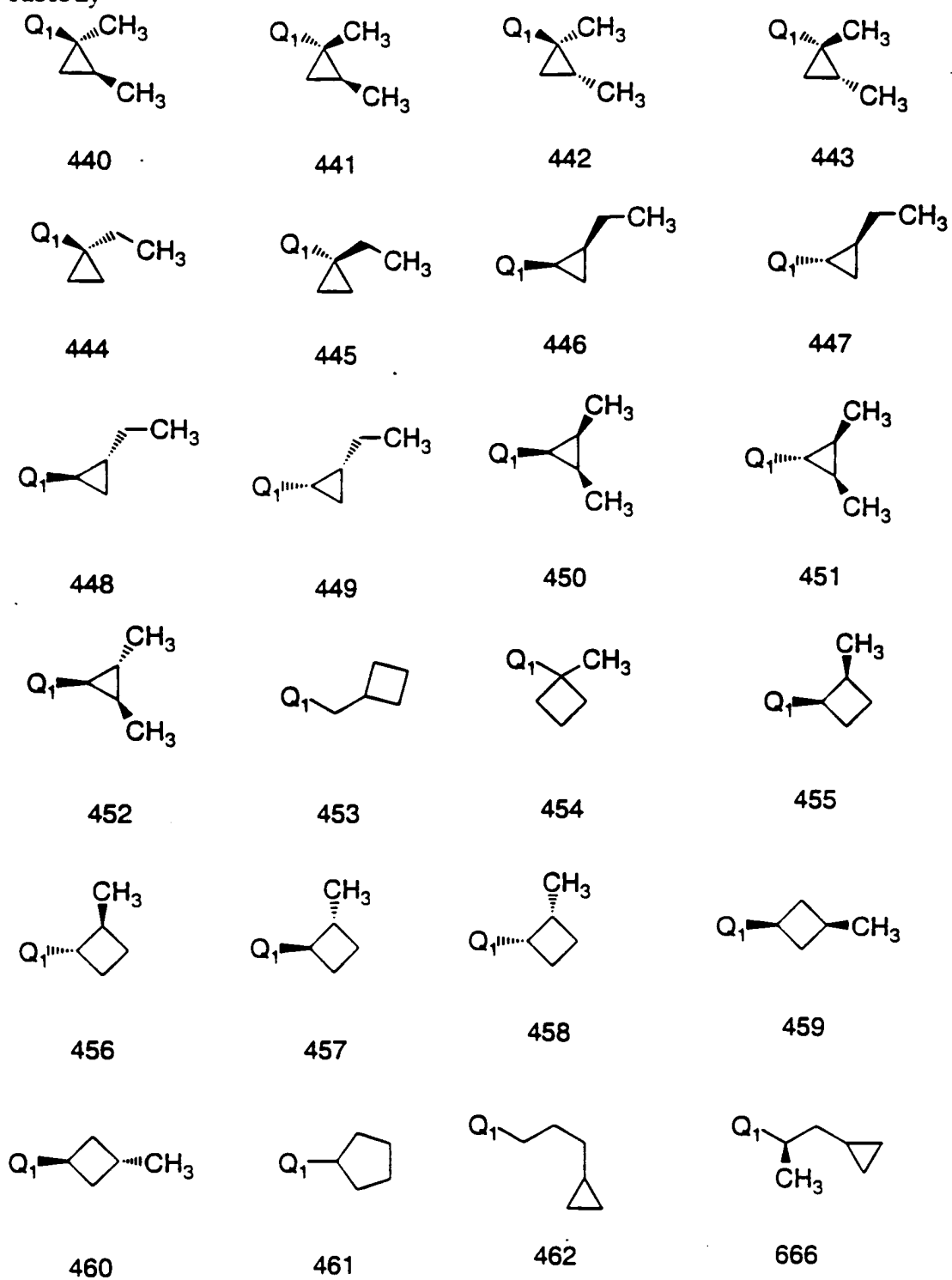


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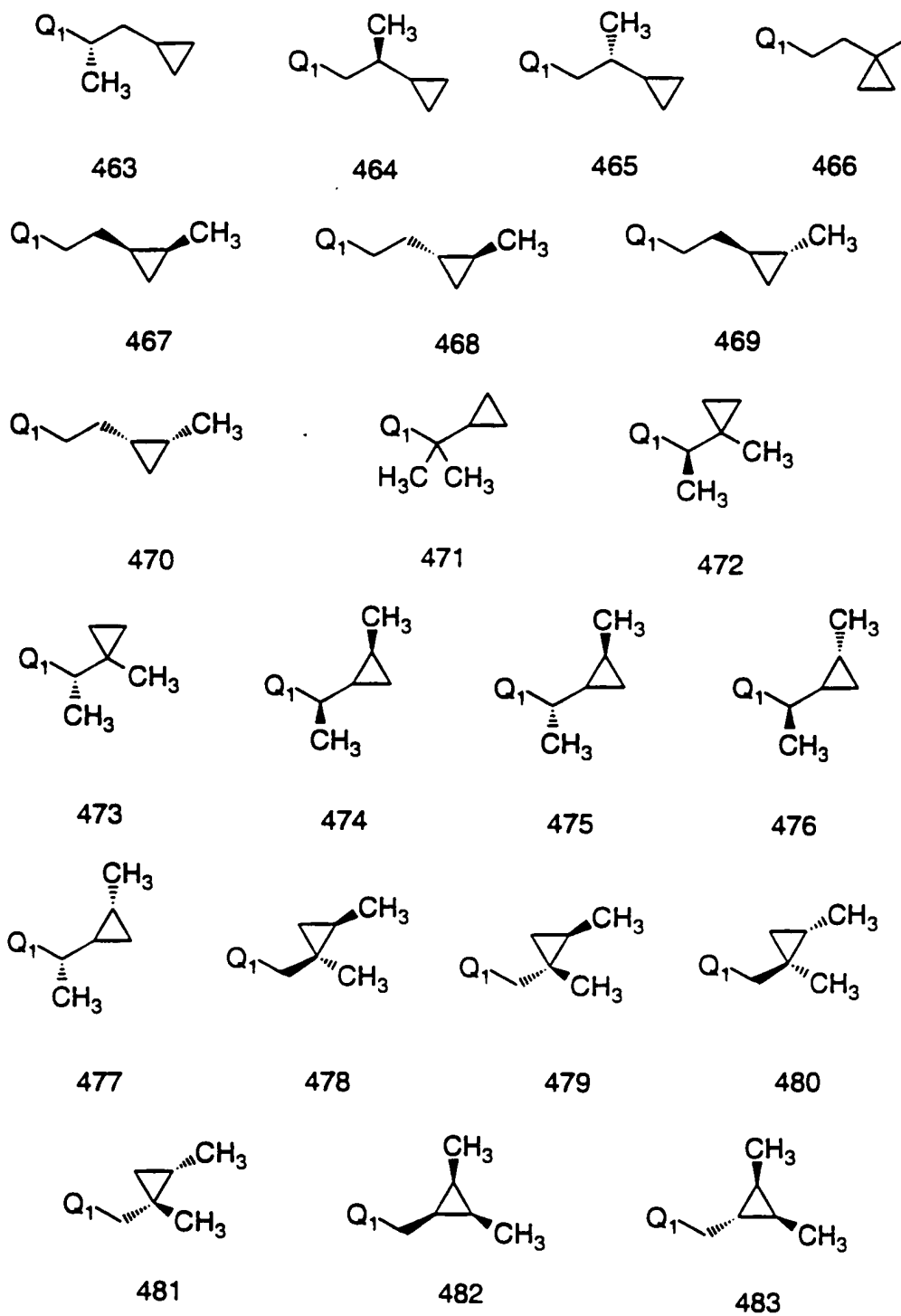


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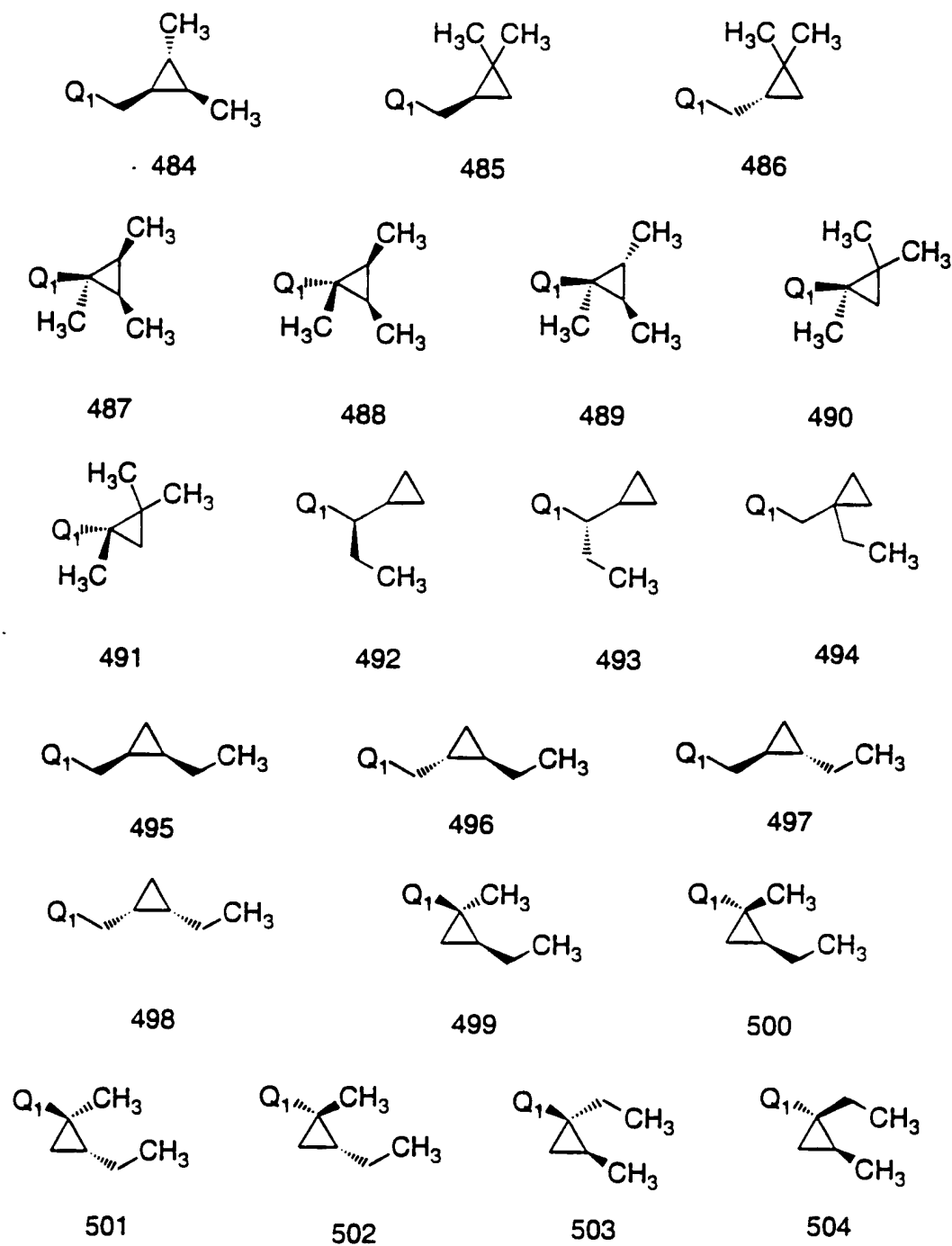


Table 2ab

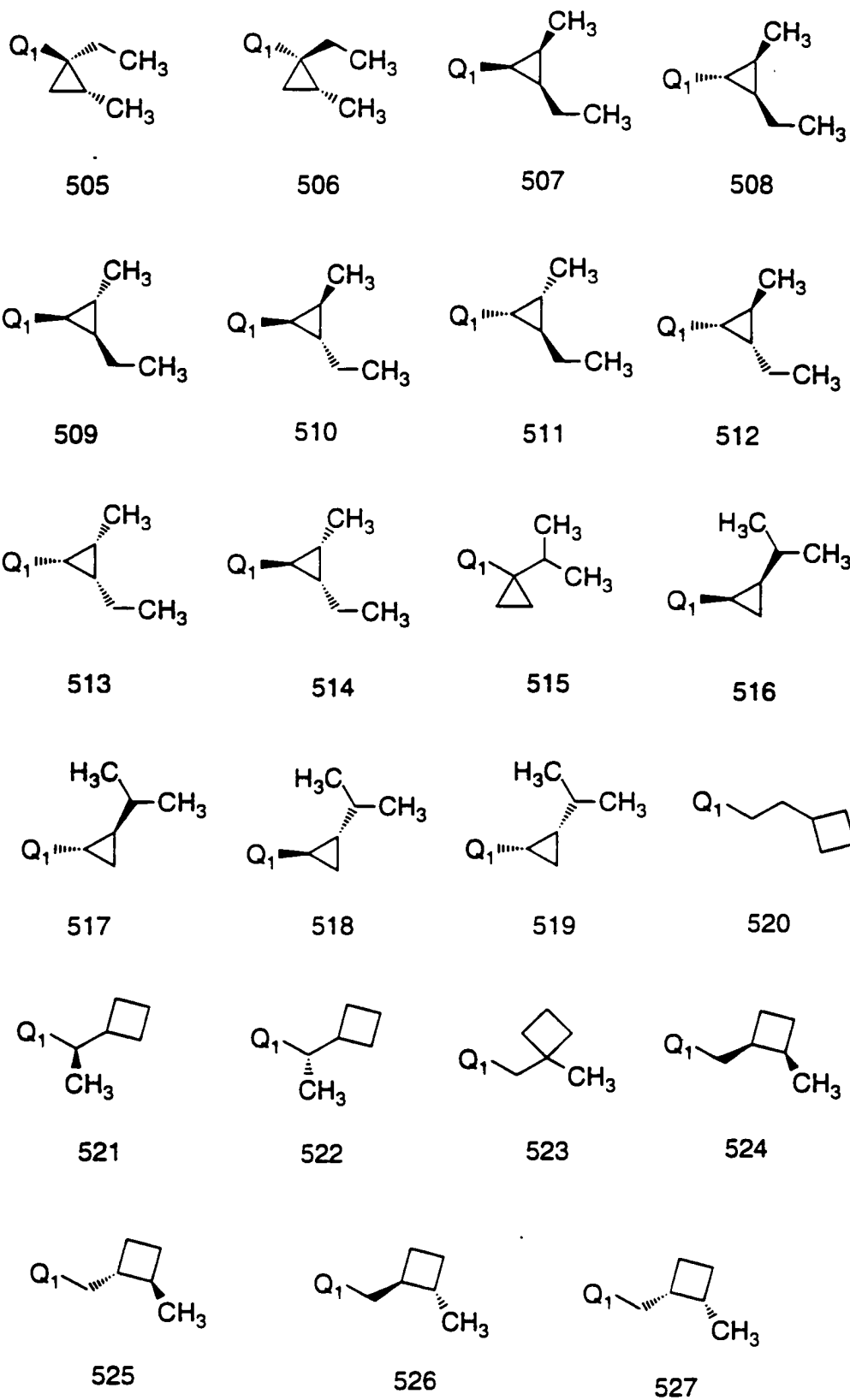


Table 2ac

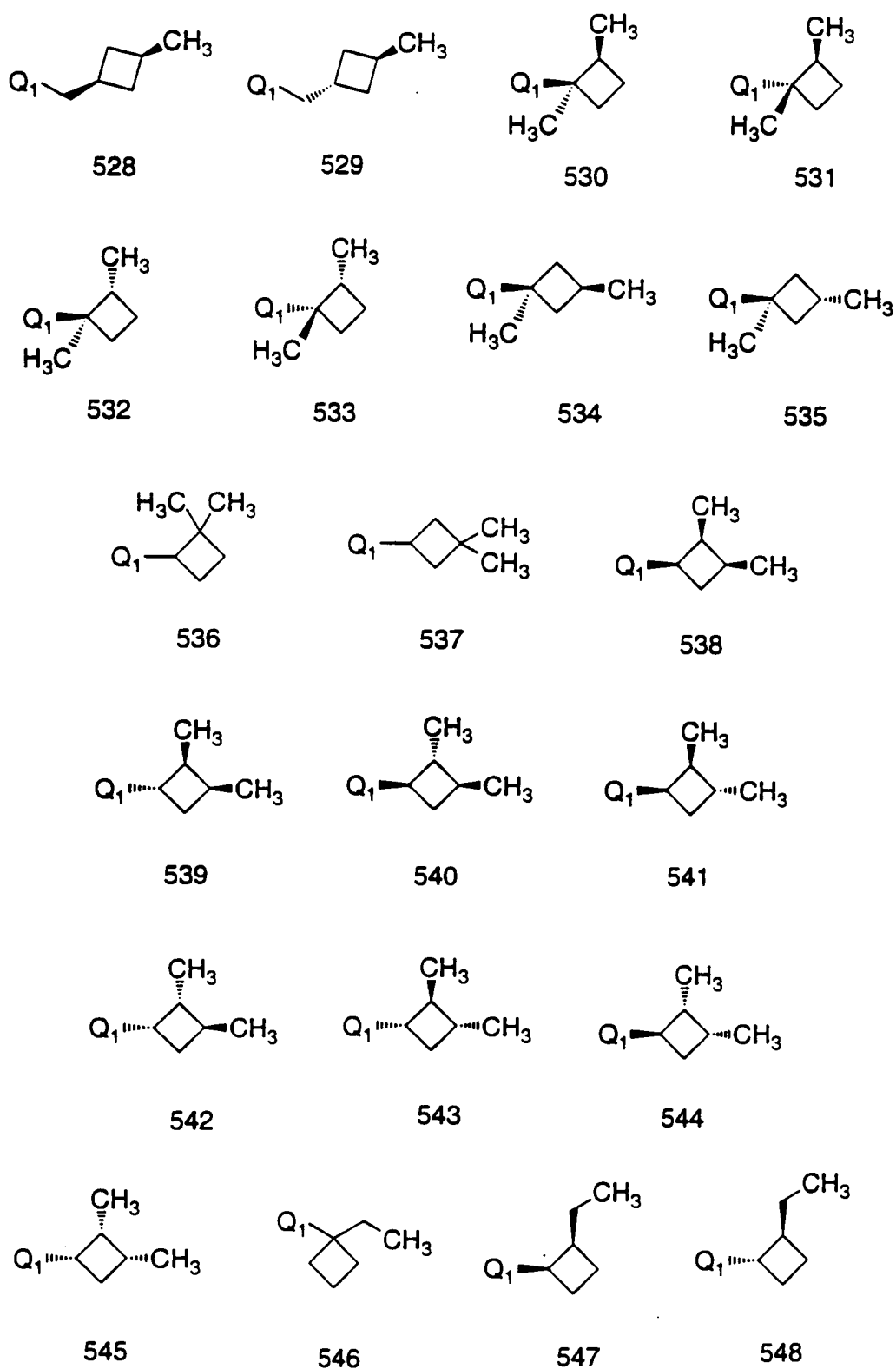


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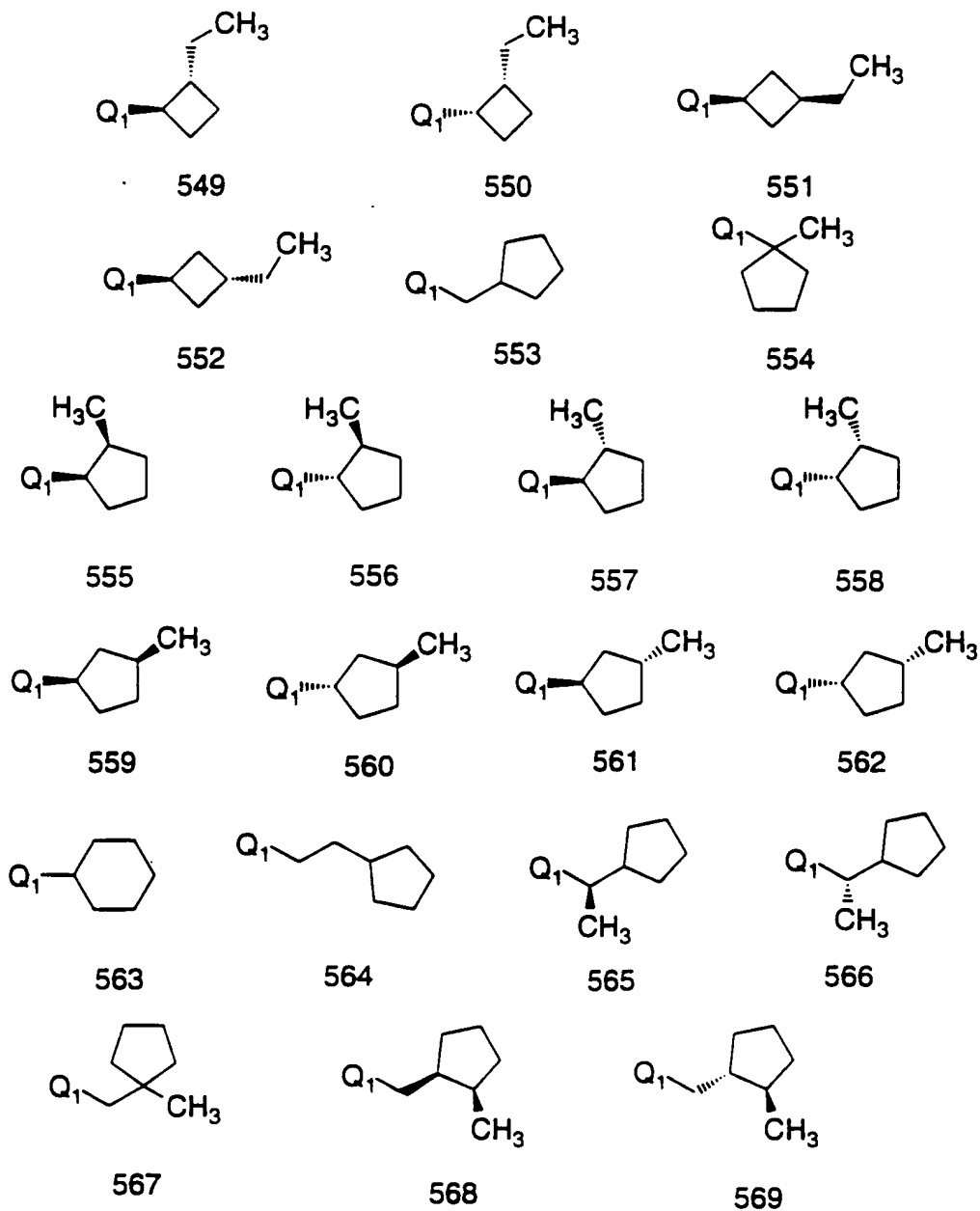
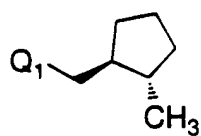
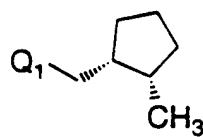


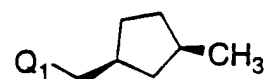
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570



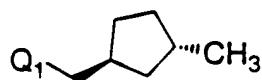
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572



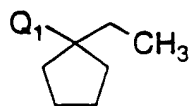
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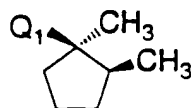
574



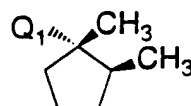
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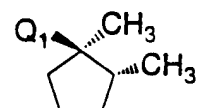
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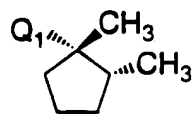
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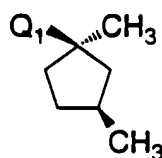
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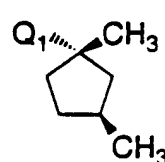
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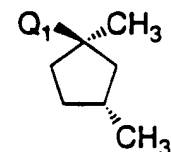
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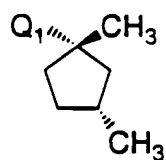
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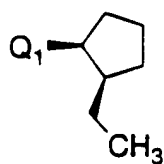
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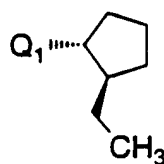
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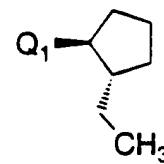
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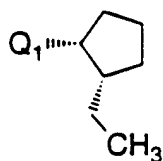
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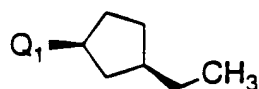
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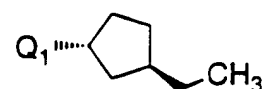
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588

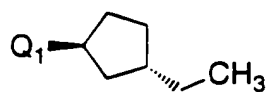


589

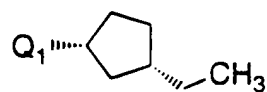


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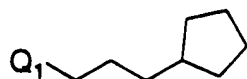
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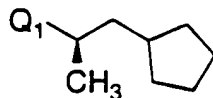
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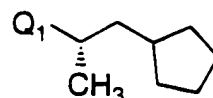
592



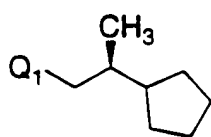
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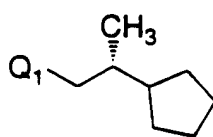
594



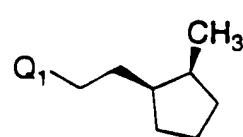
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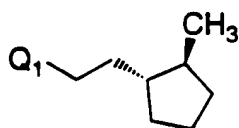
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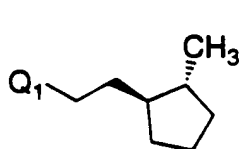
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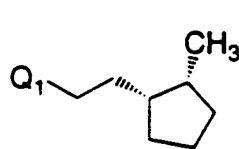
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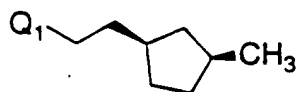
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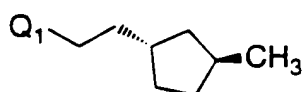
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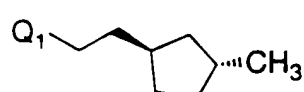
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602



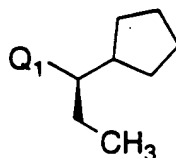
603



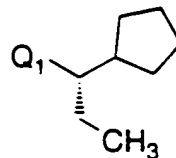
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605

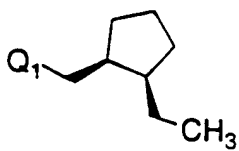


606

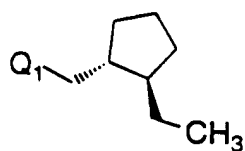


607

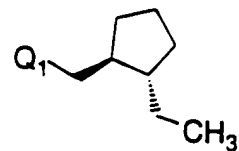
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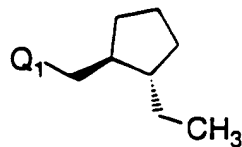
608



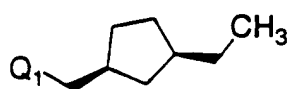
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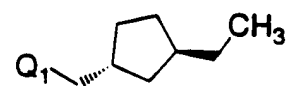
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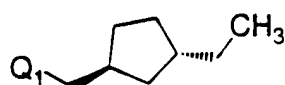
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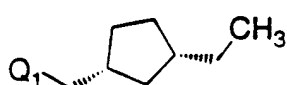
612



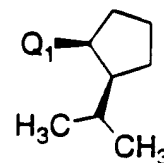
613



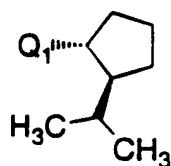
614



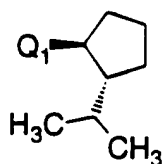
615



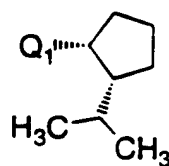
616



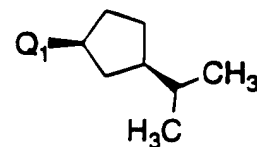
617



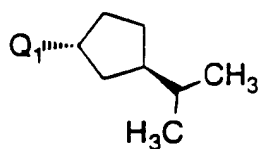
618



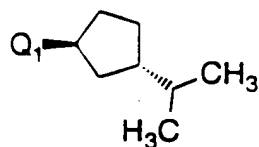
619



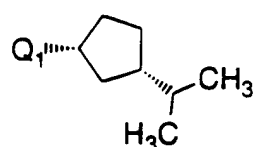
620



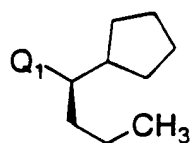
621



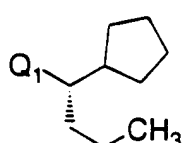
622



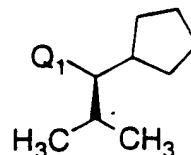
623



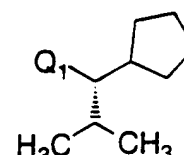
624



625

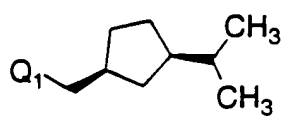


626

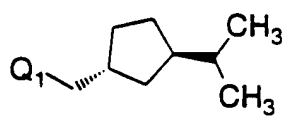


627

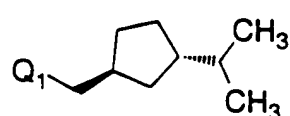
Table 2ah



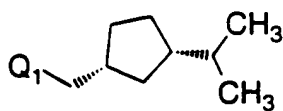
628



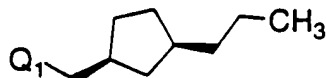
629



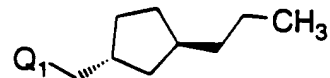
630



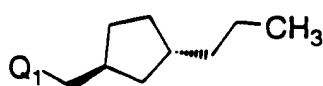
631



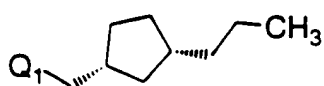
632



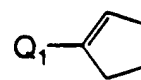
633



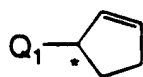
634



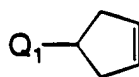
635



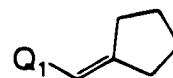
636



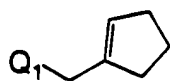
637



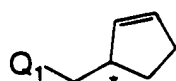
638



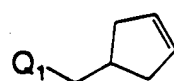
639



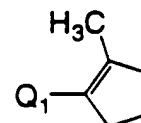
640



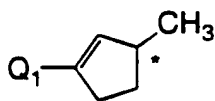
641



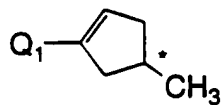
642



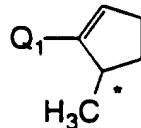
643



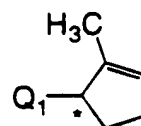
644



645

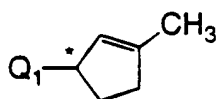


646

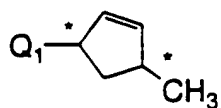


647

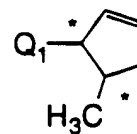
Table 2ai



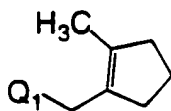
648



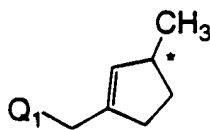
649



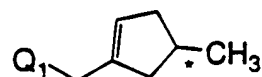
650



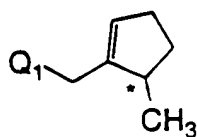
651



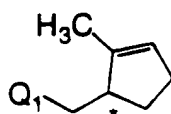
652



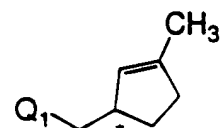
653



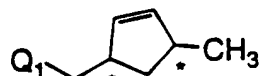
654



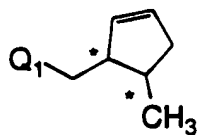
655



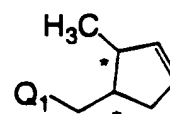
656



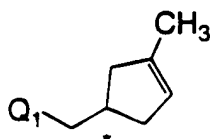
657



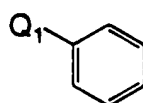
658



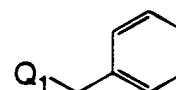
659



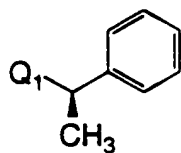
660



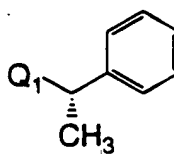
661



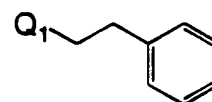
662



663

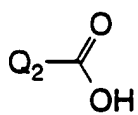


664

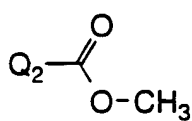


665

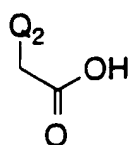
Table 3a



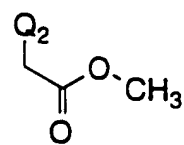
a



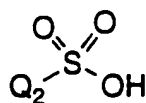
b



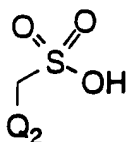
c



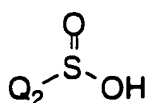
d



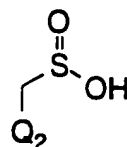
e



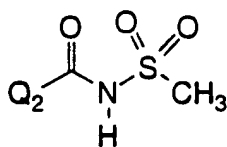
f



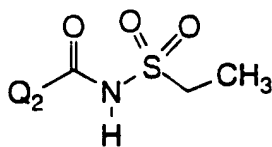
g



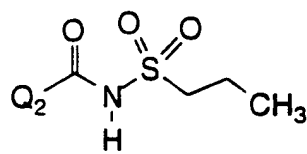
h



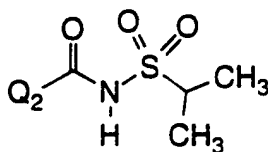
i



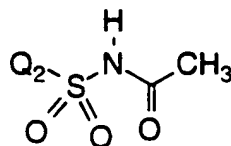
j



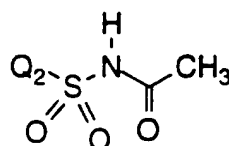
k



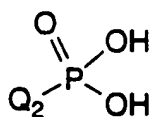
l



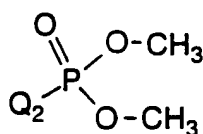
m



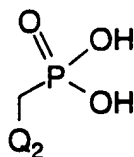
n



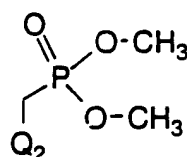
o



p

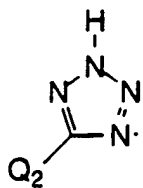


q

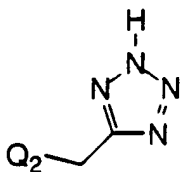


r

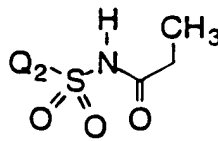
Table 3b



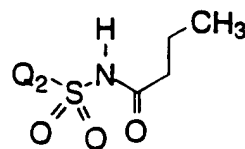
s



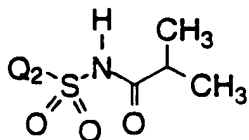
t



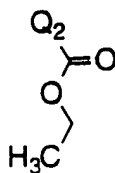
u



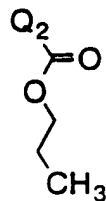
v



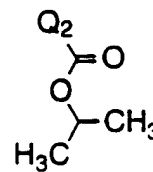
w



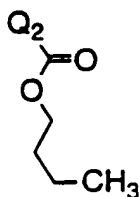
x



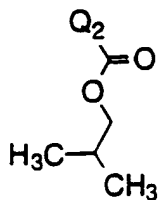
y



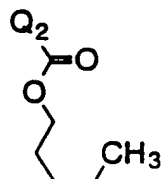
z



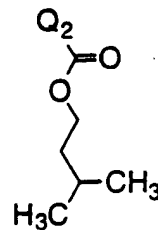
A



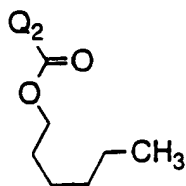
B



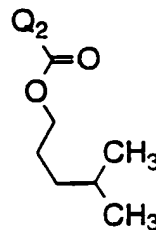
C



D



E

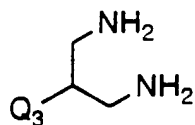


F

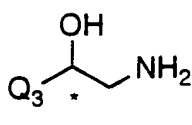
Table 4a

Q_3-OH	Q_3-N_3	Q_3-NO_2	Q_3-NH_2
1	2	3	4
5	6	7	8
9	10	11	12
13	14	15	16
17	18	19	20
21	22	23	24

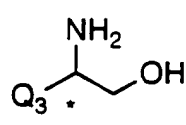
Table 4b



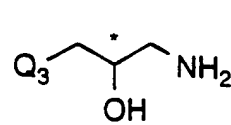
25



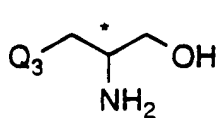
26



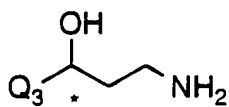
27



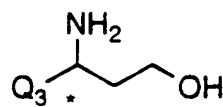
28



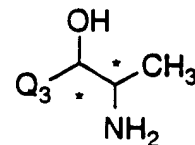
29



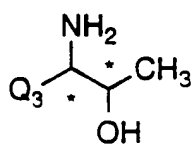
30



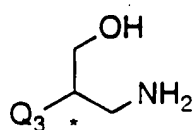
31



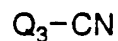
32



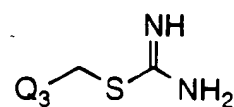
33



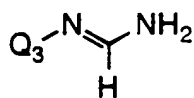
34



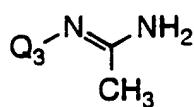
35



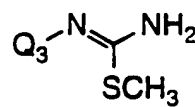
36



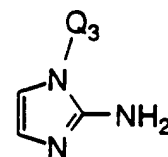
37



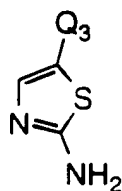
38



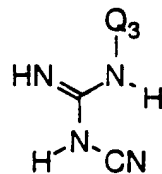
39



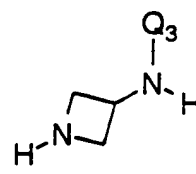
40



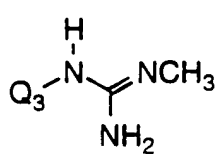
41



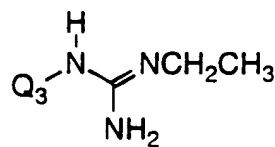
42



43

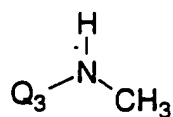


44

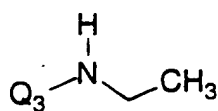


45

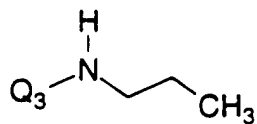
Table 4c



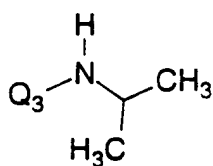
46



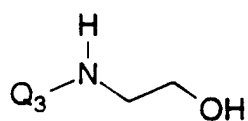
47



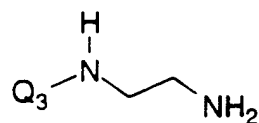
48



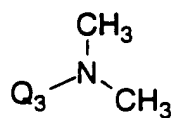
49



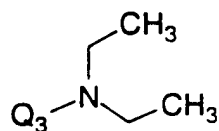
50



51



52



53

Table 5a

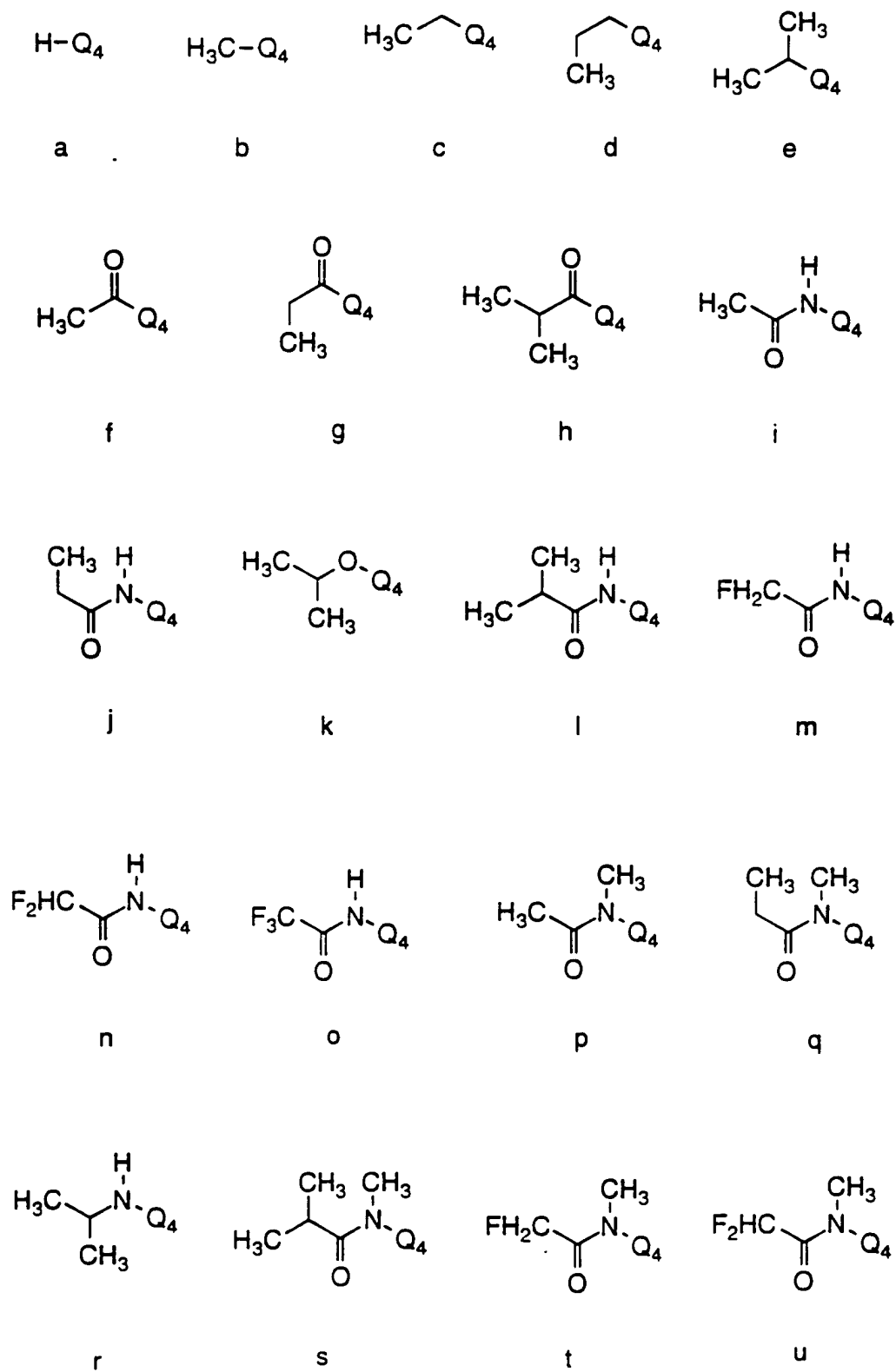
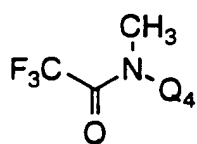
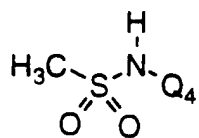


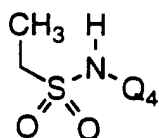
Table 5b



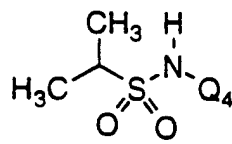
v



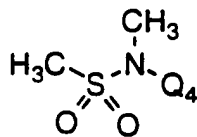
w



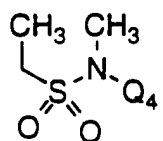
x



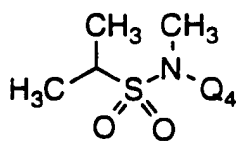
y



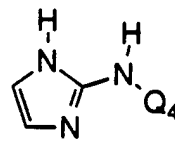
z



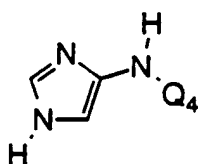
aa



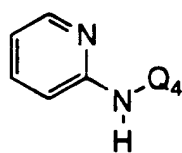
ab



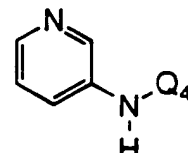
ac



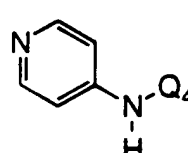
ad



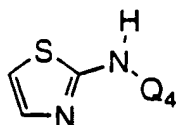
ae



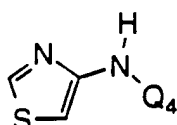
af



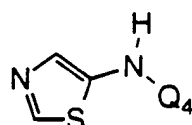
ag



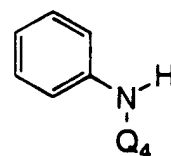
ah



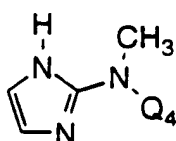
ai



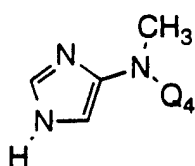
aj



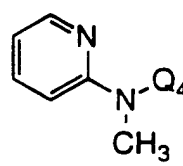
ak



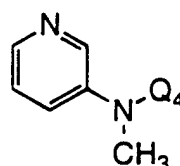
al



am



an



ao

Table 5c

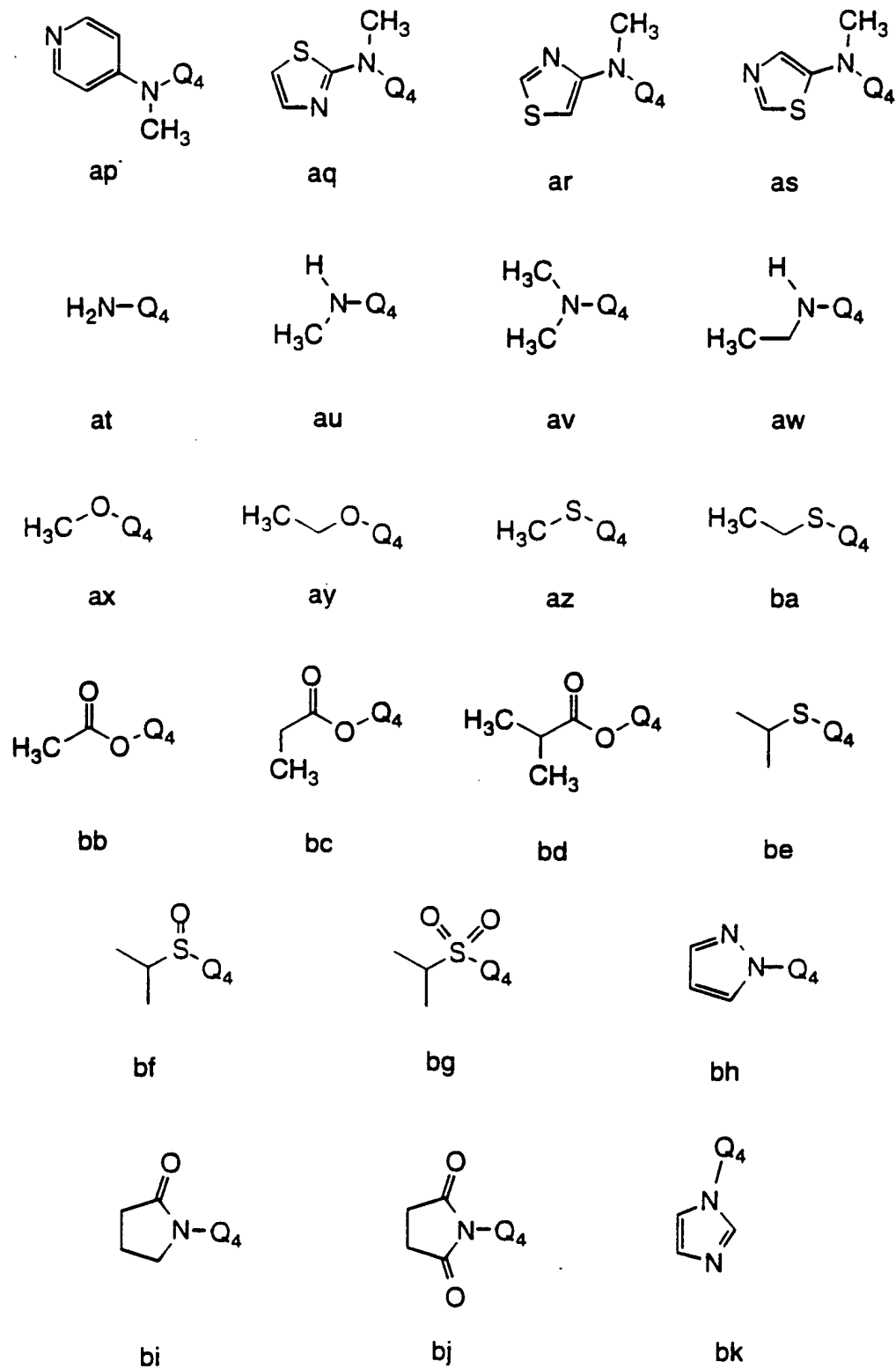


Table 6 - Exemplary Enumerated Compounds

	A.17.a.4.i; A.17.a.4.v; A.17.a.6.i; A.17.a.6.v; A.17.a.11.i; A.17.a.11.v; A.17.a.14.i;
	A.17.a.14.v; A.17.a.15.i; A.17.a.15.v; A.17.a.18.i; A.17.a.18.v; A.17.a.25.i;
5	A.17.a.25.v; A.17.e.4.i; A.17.e.4.v; A.17.e.6.i; A.17.e.6.v; A.17.e.11.i; A.17.e.11.v;
	A.17.e.14.i; A.17.e.14.v; A.17.e.15.i; A.17.e.15.v; A.17.e.18.i; A.17.e.18.v;
	A.17.e.25.i; A.17.e.25.v; A.17.g.4.i; A.17.g.4.v; A.17.g.6.i; A.17.g.6.v; A.17.g.11.i;
	A.17.g.11.v; A.17.g.14.i; A.17.g.14.v; A.17.g.15.i; A.17.g.15.v; A.17.g.18.i;
	A.17.g.18.v; A.17.g.25.i; A.17.g.25.v; A.17.l.4.i; A.17.l.4.v; A.17.l.6.i; A.17.l.6.v;
10	A.17.l.11.i; A.17.l.11.v; A.17.l.14.i; A.17.l.14.v; A.17.l.15.i; A.17.l.15.v; A.17.l.18.i;
	A.17.l.18.v; A.17.l.25.i; A.17.l.25.v; A.17.m.4.i; A.17.m.4.v; A.17.m.6.i;
	A.17.m.6.v; A.17.m.11.i; A.17.m.11.v; A.17.m.14.i; A.17.m.14.v; A.17.m.15.i;
	A.17.m.15.v; A.17.m.18.i; A.17.m.18.v; A.17.m.25.i; A.17.m.25.v; A.17.o.4.i;
	A.17.o.4.v; A.17.o.6.i; A.17.o.6.v; A.17.o.11.i; A.17.o.11.v; A.17.o.14.i;
15	A.17.o.14.v; A.17.o.15.i; A.17.o.15.v; A.17.o.18.i; A.17.o.18.v; A.17.o.25.i;
	A.17.o.25.v; A.33.a.4.i; A.33.a.4.v; A.33.a.6.i; A.33.a.6.v; A.33.a.11.i; A.33.a.11.v;
	A.33.a.14.i; A.33.a.14.v; A.33.a.15.i; A.33.a.15.v; A.33.a.18.i; A.33.a.18.v;
	A.33.a.25.i; A.33.a.25.v; A.33.e.4.i; A.33.e.4.v; A.33.e.6.i; A.33.e.6.v; A.33.e.11.i;
	A.33.e.11.v; A.33.e.14.i; A.33.e.14.v; A.33.e.15.i; A.33.e.15.v; A.33.e.18.i;
20	A.33.e.18.v; A.33.e.25.i; A.33.e.25.v; A.33.g.4.i; A.33.g.4.v; A.33.g.6.i; A.33.g.6.v;
	A.33.g.11.i; A.33.g.11.v; A.33.g.14.i; A.33.g.14.v; A.33.g.15.i; A.33.g.15.v;
	A.33.g.18.i; A.33.g.18.v; A.33.g.25.i; A.33.g.25.v; A.33.l.4.i; A.33.l.4.v; A.33.l.6.i;
	A.33.l.6.v; A.33.l.11.i; A.33.l.11.v; A.33.l.14.i; A.33.l.14.v; A.33.l.15.i; A.33.l.15.v;
	A.33.l.18.i; A.33.l.18.v; A.33.l.25.i; A.33.l.25.v; A.33.m.4.i; A.33.m.4.v;
25	A.33.m.6.i; A.33.m.6.v; A.33.m.11.i; A.33.m.11.v; A.33.m.14.i; A.33.m.14.v;
	A.33.m.15.i; A.33.m.15.v; A.33.m.18.i; A.33.m.18.v; A.33.m.25.i; A.33.m.25.v;
	A.33.o.4.i; A.33.o.4.v; A.33.o.6.i; A.33.o.6.v; A.33.o.11.i; A.33.o.11.v; A.33.o.14.i;
	A.33.o.14.v; A.33.o.15.i; A.33.o.15.v; A.33.o.18.i; A.33.o.18.v; A.33.o.25.i;
	A.33.o.25.v; A.49.a.4.i; A.49.a.4.v; A.49.a.6.i; A.49.a.6.v; A.49.a.11.i; A.49.a.11.v;
30	A.49.a.14.i; A.49.a.14.v; A.49.a.15.i; A.49.a.15.v; A.49.a.18.i; A.49.a.18.v;
	A.49.a.25.i; A.49.a.25.v; A.49.e.4.i; A.49.e.4.v; A.49.e.6.i; A.49.e.6.v; A.49.e.11.i;
	A.49.e.11.v; A.49.e.14.i; A.49.e.14.v; A.49.e.15.i; A.49.e.15.v; A.49.e.18.i;
	A.49.e.18.v; A.49.e.25.i; A.49.e.25.v; A.49.g.4.i; A.49.g.4.v; A.49.g.6.i; A.49.g.6.v;
	A.49.g.11.i; A.49.g.11.v; A.49.g.14.i; A.49.g.14.v; A.49.g.15.i; A.49.g.15.v;
35	A.49.g.18.i; A.49.g.18.v; A.49.g.25.i; A.49.g.25.v; A.49.l.4.i; A.49.l.4.v; A.49.l.6.i;
	A.49.l.6.v; A.49.l.11.i; A.49.l.11.v; A.49.l.14.i; A.49.l.14.v; A.49.l.15.i; A.49.l.15.v;
	A.49.l.18.i; A.49.l.18.v; A.49.l.25.i; A.49.l.25.v; A.49.m.4.i; A.49.m.4.v;
	A.49.m.6.i; A.49.m.6.v; A.49.m.11.i; A.49.m.11.v; A.49.m.14.i; A.49.m.14.v;
	A.49.m.15.i; A.49.m.15.v; A.49.m.18.i; A.49.m.18.v; A.49.m.25.i; A.49.m.25.v;
40	A.49.o.4.i; A.49.o.4.v; A.49.o.6.i; A.49.o.6.v; A.49.o.11.i; A.49.o.11.v; A.49.o.14.i;
	A.49.o.14.v; A.49.o.15.i; A.49.o.15.v; A.49.o.18.i; A.49.o.18.v; A.49.o.25.i;
	A.49.o.25.v; B.17.a.4.i; B.17.a.4.v; B.17.a.6.i; B.17.a.6.v; B.17.a.11.i; B.17.a.11.v;
	B.17.a.14.i; B.17.a.14.v; B.17.a.15.i; B.17.a.15.v; B.17.a.18.i; B.17.a.18.v; B.17.a.25.i;
	B.17.a.25.v; B.17.e.4.i; B.17.e.4.v; B.17.e.6.i; B.17.e.6.v; B.17.e.11.i; B.17.e.11.v;
45	B.17.e.14.i; B.17.e.14.v; B.17.e.15.i; B.17.e.15.v; B.17.e.18.i; B.17.e.18.v; B.17.e.25.i;
	B.17.e.25.v; B.17.g.4.i; B.17.g.4.v; B.17.g.6.i; B.17.g.6.v; B.17.g.11.i; B.17.g.11.v;

- B.17.g.14.i; B.17.g.14.v; B.17.g.15.i; B.17.g.15.v; B.17.g.18.i; B.17.g.18.v; B.17.g.25.i; B.17.g.25.v; B.17.l.4.i; B.17.l.4.v; B.17.l.6.i; B.17.l.6.v; B.17.l.11.i; B.17.l.11.v; B.17.l.14.i; B.17.l.14.v; B.17.l.15.i; B.17.l.15.v; B.17.l.18.i; B.17.l.18.v; B.17.l.25.i; B.17.l.25.v; B.17.m.4.i; B.17.m.4.v; B.17.m.6.i; B.17.m.6.v; B.17.m.11.i;
- 5 B.17.m.11.v; B.17.m.14.i; B.17.m.14.v; B.17.m.15.i; B.17.m.15.v; B.17.m.18.i; B.17.m.18.v; B.17.m.25.i; B.17.m.25.v; B.17.o.4.i; B.17.o.4.v; B.17.o.6.i; B.17.o.6.v; B.17.o.11.i; B.17.o.11.v; B.17.o.14.i; B.17.o.14.v; B.17.o.15.i; B.17.o.15.v; B.17.o.18.i; B.17.o.18.v; B.17.o.25.i; B.17.o.25.v; B.33.a.4.i; B.33.a.4.v; B.33.a.6.i; B.33.a.6.v; B.33.a.11.i; B.33.a.11.v; B.33.a.14.i; B.33.a.14.v; B.33.a.15.i; B.33.a.15.v;
- 10 B.33.a.18.i; B.33.a.18.v; B.33.a.25.i; B.33.a.25.v; B.33.e.4.i; B.33.e.4.v; B.33.e.6.i; B.33.e.6.v; B.33.e.11.i; B.33.e.11.v; B.33.e.14.i; B.33.e.14.v; B.33.e.15.i; B.33.e.15.v; B.33.e.18.i; B.33.e.18.v; B.33.e.25.i; B.33.e.25.v; B.33.g.4.i; B.33.g.4.v; B.33.g.6.i; B.33.g.6.v; B.33.g.11.i; B.33.g.11.v; B.33.g.14.i; B.33.g.14.v; B.33.g.15.i; B.33.g.15.v; B.33.g.18.i; B.33.g.18.v; B.33.g.25.i; B.33.g.25.v; B.33.l.4.i; B.33.l.4.v; B.33.l.6.i;
- 15 B.33.l.6.v; B.33.l.11.i; B.33.l.11.v; B.33.l.14.i; B.33.l.14.v; B.33.l.15.i; B.33.l.15.v; B.33.l.18.i; B.33.l.18.v; B.33.l.25.i; B.33.l.25.v; B.33.m.4.i; B.33.m.4.v; B.33.m.6.i; B.33.m.6.v; B.33.m.11.i; B.33.m.11.v; B.33.m.14.i; B.33.m.14.v; B.33.m.15.i; B.33.m.15.v; B.33.m.18.i; B.33.m.18.v; B.33.m.25.i; B.33.m.25.v; B.33.o.4.i; B.33.o.4.v; B.33.o.6.i; B.33.o.6.v; B.33.o.11.i; B.33.o.11.v; B.33.o.14.i; B.33.o.14.v;
- 20 B.33.o.15.i; B.33.o.15.v; B.33.o.18.i; B.33.o.18.v; B.33.o.25.i; B.33.o.25.v; B.49.a.4.i; B.49.a.4.v; B.49.a.6.i; B.49.a.6.v; B.49.a.11.i; B.49.a.11.v; B.49.a.14.i; B.49.a.14.v; B.49.a.15.i; B.49.a.15.v; B.49.a.18.i; B.49.a.18.v; B.49.a.25.i; B.49.a.25.v; B.49.e.4.i; B.49.e.4.v; B.49.e.6.i; B.49.e.6.v; B.49.e.11.i; B.49.e.11.v; B.49.e.14.i; B.49.e.14.v; B.49.e.15.i; B.49.e.15.v; B.49.e.18.i; B.49.e.18.v; B.49.e.25.i; B.49.e.25.v; B.49.g.4.i;
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- A.129.E.48.i; A.130.E.48.i; A.131.E.48.i; A.132.E.48.i; A.133.E.48.i; A.134.E.48.i;
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 A.138.F.51.i; A.139.F.51.i; A.140.F.51.i; A.141.F.51.i;

Salts and Hydrates

The compositions of this invention optionally comprise salts of the
 compounds herein, especially pharmaceutically acceptable non-toxic salts
 30 containing, for example, Na⁺, Li⁺, K⁺, Ca⁺⁺ and Mg⁺⁺. Such salts may
 include those derived by combination of appropriate cations such as alkali
 and alkaline earth metal ions or ammonium and quaternary amino ions with
 an acid anion moiety, typically the W₁ group carboxylic acid. Monovalent
 salts are preferred if a water soluble salt is desired.

35 Metal salts typically are prepared by reacting the metal hydroxide with a
 compound of this invention. Examples of metal salts which are prepared in
 this way are salts containing Li⁺, Na⁺, and K⁺. A less soluble metal salt can
 be precipitated from the solution of a more soluble salt by addition of the
 suitable metal compound.

40 In addition, salts may be formed from acid addition of certain organic
 and inorganic acids, e.g., HCl, HBr, H₂SO₄, or organic sulfonic acids, to basic
 centers, typically amines of group G₁, or to acidic groups such as E₁. Finally, it

is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the
5 parental compounds with one or more amino acids. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine,
10 isoleucine, or leucine.

Methods of Inhibition of Neuraminidase.

Another aspect of the invention relates to methods of inhibiting the activity of neuraminidase comprising the step of treating a sample suspected
15 of containing neuraminidase with a compound of the invention.

Compositions of the invention act as inhibitors of neuraminidase, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of neuraminidase having a geometry unique to neuraminidase. Compositions
20 binding neuraminidase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of neuraminidase. Accordingly, the invention relates to methods of detecting neuraminidase in
25 a sample suspected of containing neuraminidase comprising the steps of: treating a sample suspected of containing neuraminidase with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores,
30 radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl or amino.

Within the context of the invention samples suspected of containing neuraminidase include natural or man-made materials such as living
35 organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum,

saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces neuraminidase, frequently a pathogenic organism such as a virus. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of neuraminidase after application of the composition can be observed by any method including direct and indirect methods of detecting neuraminidase activity. Quantitative, qualitative, and semiquantitative methods of determining neuraminidase activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain neuraminidase include bacteria (*Vibrio cholerae*, *Clostridium perfringens*, *Streptococcus pneumoniae*, and *Arthrobacter sialophilus*) and viruses (especially orthomyxoviruses or paramyxoviruses such as influenza virus A and B, parainfluenza virus, mumps virus, Newcastle disease virus, fowl plague virus, and sendai virus). Inhibition of neuraminidase activity obtained from or found within any of these organisms is within the objects of this invention. The virology of influenza viruses is described in "Fundamental Virology" (Raven Press, New York, 1986), Chapter 24. The compounds of this invention are useful in the treatment or prophylaxis of such infections in animals, e.g. duck, rodents, or swine, or in man.

However, in screening compounds capable of inhibiting influenza viruses it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays, as shown Table 1 of Chandler et al., supra. Thus, a plaque reduction assay should be the primary screening tool.

Screens for Neuraminidase Inhibitors.

Compositions of the invention are screened for inhibitory activity against neuraminidase by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of neuraminidase *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* K_i (inhibitory constants) of less than about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, Itzstein, M. von et al.; "Nature", 363(6428):418-423 (1993), in particular page 420, column 2, full paragraph 3, to page 421, column 2, first partial paragraph, describes a suitable *in vitro* assay of Potier, M.; et al.; "Analyt. Biochem.", 94:287-296 (1979), as modified by Chong, A.K.J.; et al.; "Biochem. Biophys. Acta", 1077:65-71 (1991); and Colman, P. M.; et al.; International Publication No. WO 92/06691 (Int. App. No. PCT/AU90/00501, publication date April 30, 1992) page 34, line 13, to page 35, line 16, describes another useful *in vitro* screen.

In vivo screens have also been described in detail, see Itzstein, M. von et al.; *op. cit.*, in particular page 421, column 2, first full paragraph, to page 423, column 2, first partial paragraph, and Colman, P. M.; et al.; *op. cit.* page 36, lines 1-38, describe suitable *in vivo* screens.

Pharmaceutical Formulations and Routes of Administration.

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally; it is not necessary to administer them by intrapulmonary or intranasal routes.

Surprisingly, the anti-influenza compounds of WO 91/16320, WO 92/06691 and U.S. Patent 5,360,817 are successfully administered by the oral or intraperitoneal routes. See Example 161 infra.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration are prepared as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as

an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by
5 compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may
10 optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20%
15 w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be
20 formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures
25 thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted
30 from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also
35 preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax

together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween[®] 60, Span[®] 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry

powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of influenza A or B infections as described below.

5 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

10 Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

15 The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage
20 formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

25 It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

30 The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

35 Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active influenza infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, for inhalation the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Active ingredients of the invention are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmacoproperties of the combination. For example, when treating viral infections of the respiratory system, in particular influenza infection, the compositions of the invention are combined with antivirals (such as amantidine, rimantadine and ribavirin), mucolytics, expectorants, bronchialdilators, antibiotics, antipyretics, or analgesics. Ordinarily, antibiotics, antipyretics, and analgesics are administered together with the compounds of this invention.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and

unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. C¹⁴ or H³) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no neuraminidase inhibitory activity of their own.

Additional Uses for the Compounds of This Invention.

The compounds of this invention, or the biologically active substances produced from these compounds by hydrolysis or metabolism *in vivo*, are used as immunogens or for conjugation to proteins, whereby they serve as components of immunogenic compositions to prepare antibodies capable of binding specifically to the protein, to the compounds or to their metabolic products which retain immunologically recognized epitopes (sites of antibody binding). The immunogenic compositions therefore are useful as intermediates in the preparation of antibodies for use in diagnostic, quality control, or the like, methods or in assays for the compounds or their novel metabolic products. The compounds are useful for raising antibodies against otherwise non-immunogenic polypeptides, in that the compounds serve as haptenic sites stimulating an immune response that cross-reacts with the unmodified conjugated protein.

The hydrolysis products of interest include products of the hydrolysis of the protected acidic and basic groups discussed above. As noted above, the acidic or basic amides comprising immunogenic polypeptides such as albumin or keyhole limpet hemocyanin generally are useful as immunogens.

The metabolic products described above may retain a substantial degree of immunological cross reactivity with the compounds of the invention. Thus, the antibodies of this invention will be capable of binding to the unprotected compounds of the invention without binding to the protected compounds; alternatively the metabolic products, will be capable of binding to the protected compounds and/or the metabolic products without binding to the protected compounds of the invention, or will be capable of binding specifically to any one or all three. The antibodies desirably will not substantially cross-react with naturally-occurring materials. Substantial cross-reactivity is reactivity under specific assay conditions for specific analytes sufficient to interfere with the assay results.

The immunogens of this invention contain the compound of this invention presenting the desired epitope in association with an immunogenic substance. Within the context of the invention such association means covalent bonding to form an immunogenic conjugate (when applicable) or a mixture of non-covalently bonded materials, or a combination of the above. Immunogenic substances include adjuvants such as Freund's adjuvant, immunogenic proteins such as viral, bacterial, yeast, plant and animal polypeptides, in particular keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin or soybean trypsin inhibitor, and immunogenic polysaccharides. Typically, the compound having the structure of the desired epitope is covalently conjugated to an immunogenic polypeptide or polysaccharide by the use of a polyfunctional (ordinarily bifunctional) cross-linking agent. Methods for the manufacture of haptens immunogens are conventional *per se*, and any of the methods used heretofore for conjugating haptens to immunogenic polypeptides or the like are suitably employed here as well, taking into account the functional groups on the precursors or hydrolytic products which are available for cross-linking and the likelihood of producing antibodies specific to the epitope in question as opposed to the immunogenic substance.

Typically the polypeptide is conjugated to a site on the compound of the invention distant from the epitope to be recognized.

The conjugates are prepared in conventional fashion. For example, the cross-linking agents N-hydroxysuccinimide, succinic anhydride or $\text{alkN}=\text{C}=\text{Nalk}$ are useful in preparing the conjugates of this invention. The conjugates comprise a compound of the invention attached by a bond or a

linking group of 1-100, typically, 1-25, more typically 1-10 carbon atoms to the immunogenic substance. The conjugates are separated from starting materials and by products using chromatography or the like, and then are sterile filtered and vialled for storage.

5 The compounds of this invention are cross-linked for example through any one or more of the following groups: a hydroxyl group of U₁; a carboxyl group of E₁; a carbon atom of U₁, E₁, G₁, or T₁, in substitution of H; and an amine group of G₁. Included within such compounds are amides of polypeptides where the polypeptide serves as an above-described R_{6c} or R_{6b}
10 groups.

Animals are typically immunized against the immunogenic conjugates or derivatives and antisera or monoclonal antibodies prepared in conventional fashion.

15 The compounds of the invention are useful for maintaining the structural integrity of glycoproteins in recombinant cell culture, i.e., they are added to fermentations in which glycoproteins are being produced for recovery so as to inhibit neuraminidase-catalyzed cleavage of the desired glycoproteins. This is of particular value in the recombinant synthesis of proteins in heterologous host cells that may disadvantageously degrade the
20 carbohydrate portion of the protein being synthesized.

The compounds of the invention are polyfunctional. As such they represent a unique class of monomers for the synthesis of polymers. By way of example and not limitation, the polymers prepared from the compounds of this invention include polyamides and polyesters.

25 The present compounds are used as monomers to provide access to polymers having unique pendent functionalities. The compounds of this invention are useful in homopolymers, or as comonomers with monomers which do not fall within the scope of the invention. Homopolymers of the compounds of this invention will have utility as cation exchange agents
30 (polyesters or polyamides) in the preparation of molecular sieves (polyamides), textiles, fibers, films, formed articles and the like where the acid functionality E₁ is esterified to a hydroxyl group in U₁, for example, whereby the pendant basic group G₁ is capable of binding acidic functionalities such as are found in polypeptides whose purification is desired. Polyamides are
35 prepared by cross-linking E₁ and G₁, with U₁ and the adjacent portion of the ring remaining free to function as a hydrophilic or hydrophobic affinity

group, depending up the selection of the U₁ group. The preparation of these polymers from the compounds of the invention is conventional per se.

The compounds of the invention are also useful as a unique class of polyfunctional surfactants. Particularly when U₁ does not contain a hydrophilic substituent and is, for example, alkyl or alkoxy, the compounds have the properties of bi-functional surfactants. As such they have useful surfactant, surface coating, emulsion modifying, rheology modifying and surface wetting properties.

As polyfunctional compounds with defined geometry and carrying simultaneously polar and non-polar moieties, the compounds of the invention are useful as a unique class of phase transfer agents. By way of example and not limitation, the compounds of the invention are useful in phase transfer catalysis and liquid/liquid ion extraction (LIX).

The compounds of the invention optionally contain asymmetric carbon atoms in groups U₁, E₁, G₁, and T₁. As such, they are a unique class of chiral auxiliaries for use in the synthesis or resolution of other optically active materials. For example, a racemic mixture of carboxylic acids can be resolved into its component enantiomers by: 1) forming a mixture of diastereomeric esters or amides with a compound of the invention wherein U₁ is an asymmetric hydroxyalkane or amino alkane group; 2) separating the diastereomers; and 3) hydrolyzing the ester structure. Racemic alcohols are separated by ester formation with an acid group of E₁. Further, such a method can be used to resolve the compounds of the invention themselves if optically active acids or alcohols are used instead of racemic starting materials.

The compounds of this invention are useful as linkers or spacers in preparing affinity absorption matrices, immobilized enzymes for process control, or immunoassay reagents. The compounds herein contain a multiplicity of functional groups that are suitable as sites for cross-linking desired substances. For example, it is conventional to link affinity reagents such as hormones, peptides, antibodies, drugs, and the like to insoluble substrates. These insolublized reagents are employed in known fashion to absorb binding partners for the affinity reagents from manufactured preparations, diagnostic samples and other impure mixtures. Similarly, immobilized enzymes are used to perform catalytic conversions with facile recovery of enzyme. Bifunctional compounds are commonly used to link analytes to detectable groups in preparing diagnostic reagents.

Many functional groups in the compounds of this invention are suitable for use in cross-linking. For example, the carboxylic or phosphonic acid of group E₁ is used to form esters with alcohols or amides with amines of the reagent to be cross-linked. The G₁ sites substituted with OH, NHR₁, SH, azido (which is reduced to amino if desired before cross-linking), CN, NO₂, amino, guanidino, halo and the like are suitable sites. Suitable protection of reactive groups will be used where necessary while assembling the cross-linked reagent to prevent polymerization of the bifunctional compound of this invention. In general, the compounds here are used by linking them through carboxylic or phosphonic acid to the hydroxyl or amino groups of the first linked partner, then covalently bonded to the other binding partner through a T₁ or G₁ group. For example a first binding partner such as a steroid hormone is esterified to the carboxylic acid of a compound of this invention and then this conjugate is cross-linked through a G₁ hydroxyl to cyanogen bromide activated Sepharose, whereby immobilized steroid is obtained. Other chemistries for conjugation are well known. See for example Maggio, "Enzyme-Immunoassay" (CRC, 1988, pp 71-135) and references cited therein.

As noted above, the therapeutically useful compounds of this invention in which the W₁, or G₁ carboxyl, hydroxyl or amino groups are protected are useful as oral or sustained release forms. In these uses the protecting group is removed *in vivo*, e.g., hydrolyzed or oxidized, so as to yield the free carboxyl, amino or hydroxyl. Suitable esters or amides for this utility are selected based on the substrate specificity of esterases and/or carboxypeptidases expected to be found within cells where precursor hydrolysis is desired. To the extent that the specificity of these enzymes is unknown, one will screen a plurality of the compounds of this invention until the desired substrate specificity is found. This will be apparent from the appearance of free compound or of antiviral activity. One generally selects amides or esters of the invention compound that are (i) not hydrolyzed or hydrolyzed comparatively slowly in the upper gut, (ii) gut and cell permeable and (iii) hydrolyzed in the cell cytoplasm and/or systemic circulation. Screening assays preferably use cells from particular tissues that are susceptible to influenza infection, e.g. the mucous membranes of the bronchopulmonary tract. Assays known in the art are suitable for determining *in vivo* bioavailability including intestinal lumen stability, cell

permeation, liver homogenate stability and plasma stability assays. However, even if the ester, amide or other protected derivatives are not converted *in vivo* to the free carboxyl, amino or hydroxyl groups, they remain useful as chemical intermediates.

5

Exemplary Methods of Making the Compounds of the Invention.

The invention also relates to methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in "Compendium of Organic Synthetic Methods" (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., "Advanced Organic Chemistry, Third Edition", (John Wiley & Sons, New York, 1985), "Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes", Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as temperature, reaction time, solvents, workup procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Workup typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic

for oxidations. Reaction times are adjusted to achieve desired conversions.

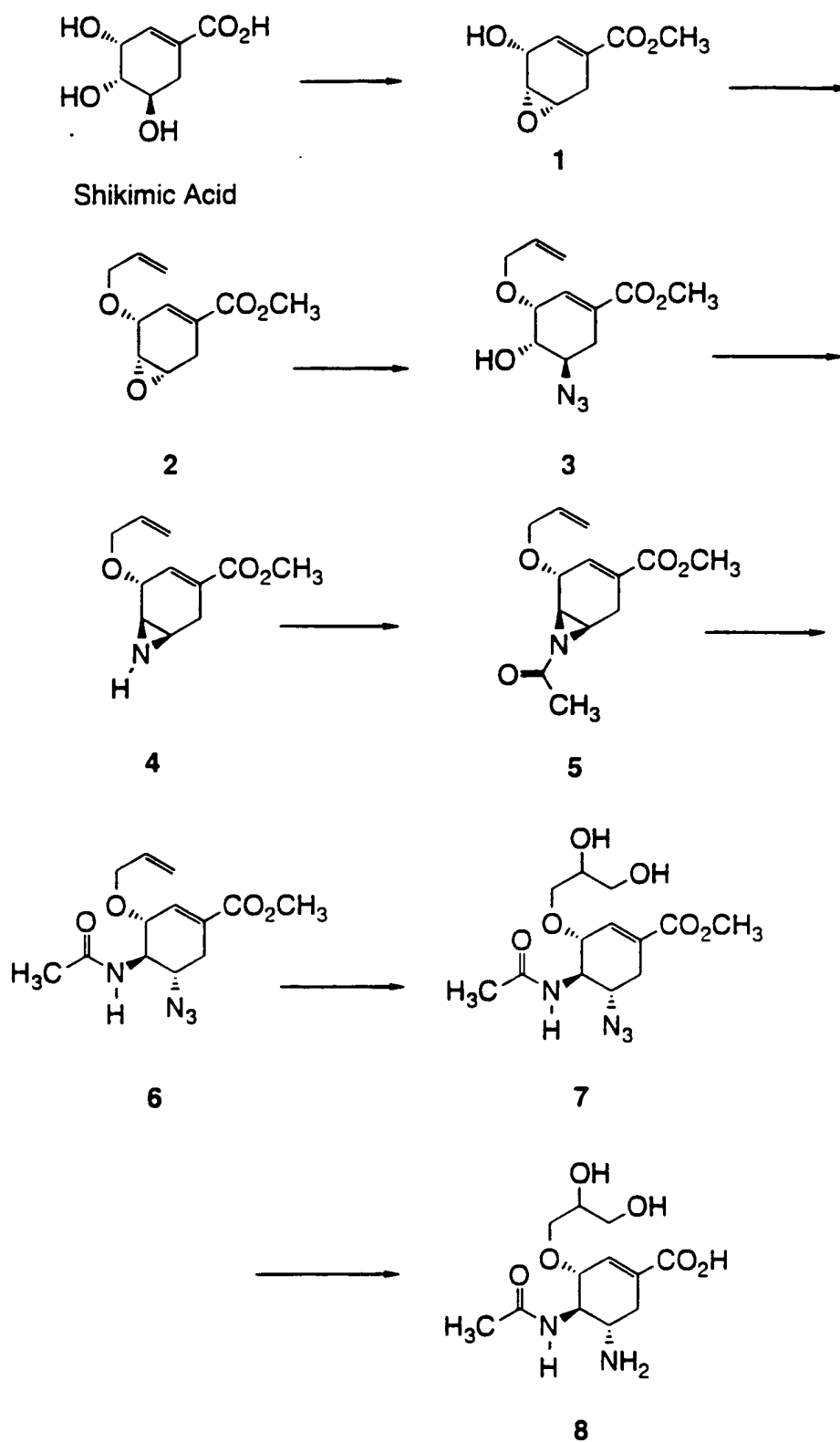
Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common.

- 5 Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and will be applied when applicable.

- 10 One exemplary method of preparing the compounds of the invention is shown in Scheme 1 below. A detailed description of the methods is found in the Experimental section below.

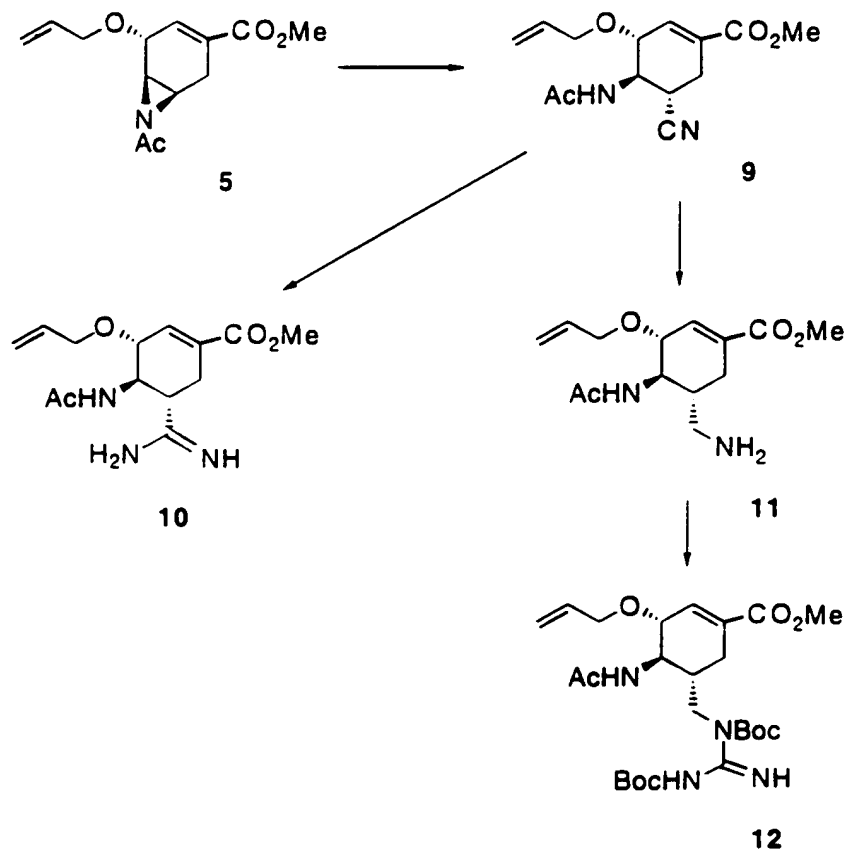
Scheme 1



Modifications of Scheme 1 to form additional embodiments is shown in Schemes 2-4.

Scheme 2

5



Scheme 2

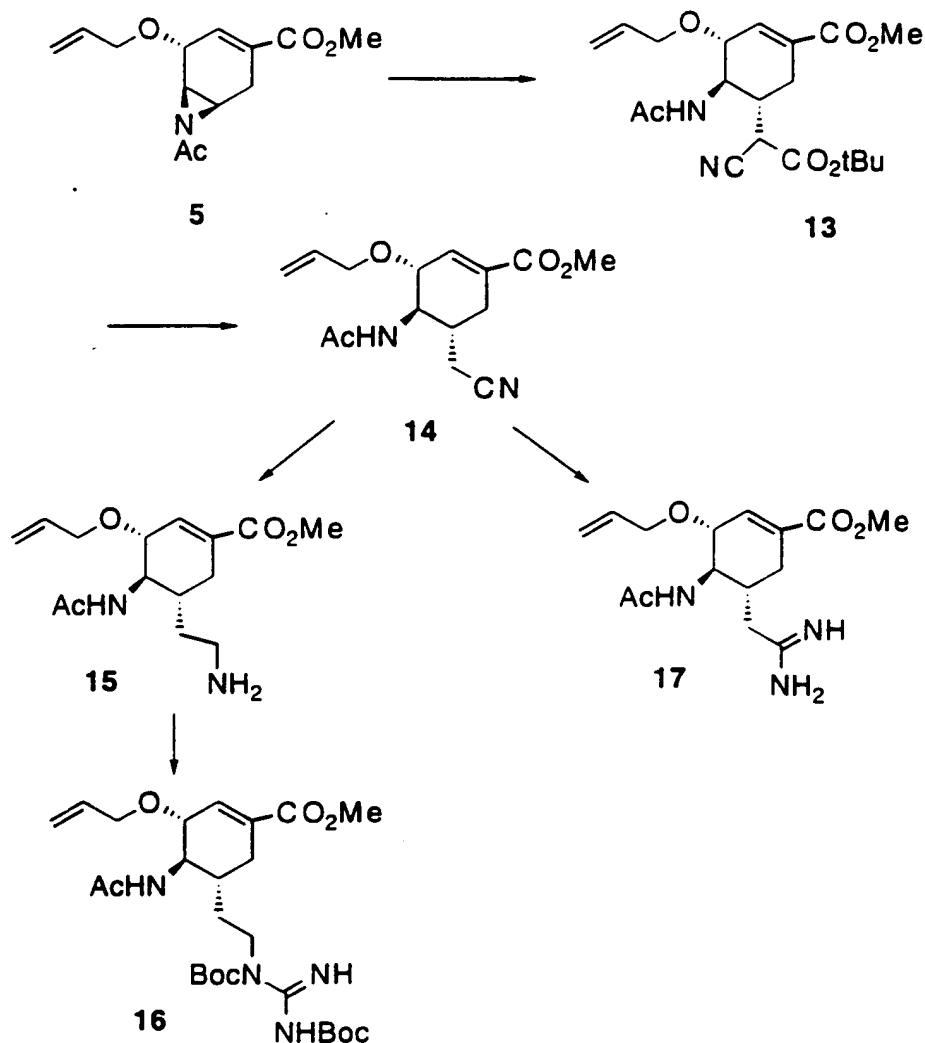
Aziridine 5 is converted to the amino nitrile 9 by $\text{Yb}(\text{CN})_3$ catalyzed addition of TMSCN according to the procedure of Utimoto and co-workers, "Tetrahedron Lett.", 31:6379 (1990).

Conversion of nitrile 9 to the corresponding amidine 10 is accomplished using a standard three step sequence: i) H_2S ; ii) CH_3I ; iii) NH_4OAc . A typical conversion is found in "J. Med. Chem.", 36:1811 (1993).

Nitrile 9 is converted to the amino methyl compound 11 by reduction using any of the available methods found in "Modern Synthetic Reactions" 2nd ed. H.O. House, Benjamin/Cummings Publishing Co., 1972.

Amino methyl compound 11 is converted to the bis-Boc protected guanidino compound 12 by treating 11 with N,N' -bis-Boc-1H-pyrazole-1-carboxamide according to the method found in "Tetrahedron Lett.", 36:299 (1995).

Scheme 3



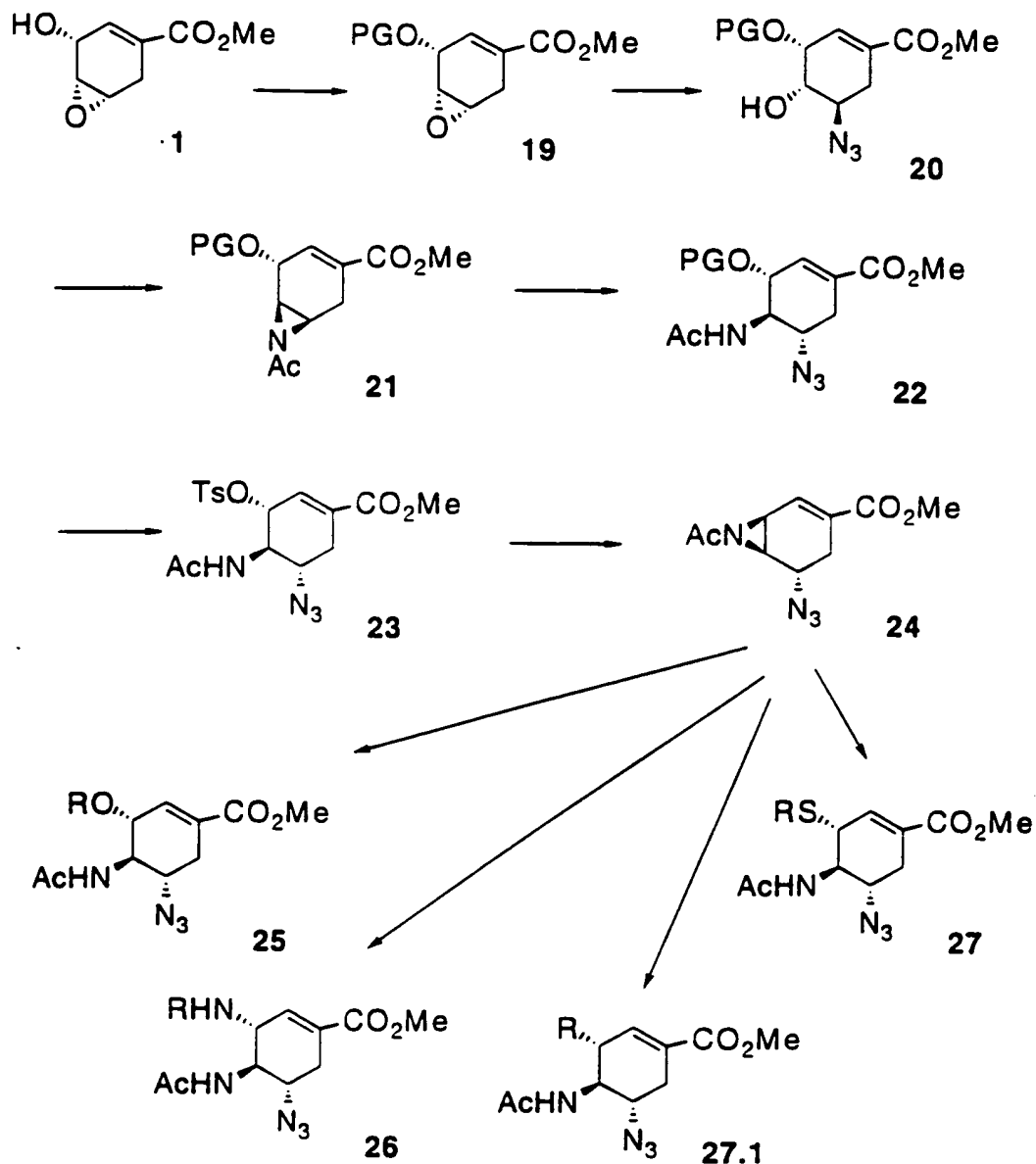
Scheme 3

5 The aziridine 5 is opened with α-cyano acetic acid t-butyl ester to give 13. Aziridine openings of this type are found in "Tetrahedron Lett.", 23:5021 (1982). Selective hydrolysis of the t-butyl ester moiety under acidic conditions followed by decarboxylation gives nitrile 14.

10 Reduction of 14 to the amino ethyl derivative 15 is accomplished in the same fashion as the conversion of 9 to 11. The amine 15 is then converted into the guanidino derivative 16 with N,N'-bis-Boc-1H-pyrazole-1-carboxamide according to the method found in "Tetrahedron Lett.", 36:299 (1995).

15 The nitrile 14 is converted to the corresponding amidine 17 using the same sequence described above for the conversion of 9 to 10.

Scheme 4

5 Scheme 4

The epoxy alcohol 1 is protected (PG=protecting group), for example with MOMCl. Typical conditions are found in "Protective Groups in Organic Synthesis" 2nd ed., T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, NY, 1991.

10 The epoxide 19 is opened with NaN₃/NH₄Cl to the amino alcohol 20

according to the procedure of Sharpless and co-workers, "J. Org. Chem.", 50:1557 (1985).

Reduction of 20 to the N-acetyl aziridine 21 is accomplished in a three step sequence: 1) MsCl/triethyl amine; 2) H₂/Pd; 3) AcCl/pyridine. Such transformations can be found in "Angew. Chem. Int. Ed. Engl.", 33:599 (1994).

Aziridine 21 is converted to the azido amide 22 by opening with NaN₃/NH₄Cl in DMF at 65 °C as described in "J. Chem. Soc. Perkin Trans I", 801 (1976).

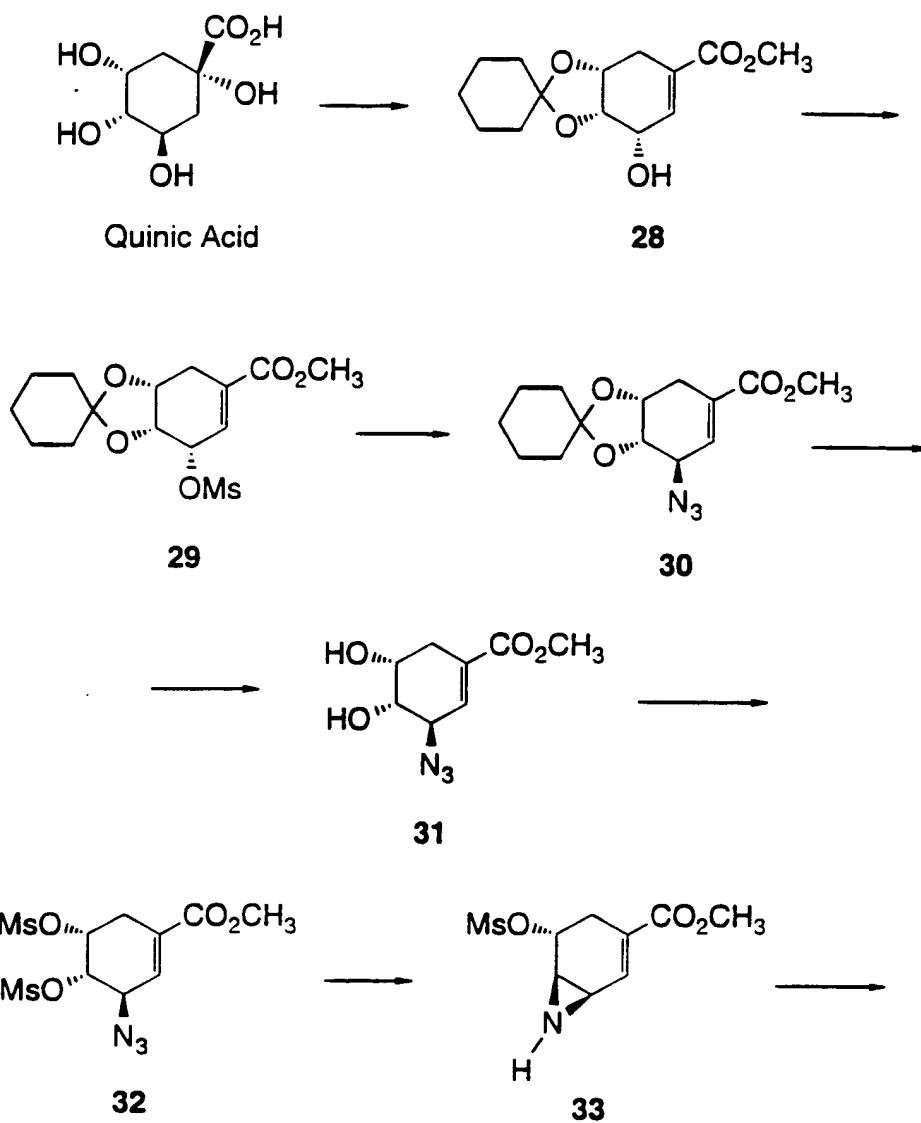
Removal of the MOM protecting group of 22 is accomplished using the methods described in "Protective Groups in Organic Synthesis" 2nd ed., T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, NY, 1991. The resulting alcohol is converted directly to aziridine 24 with TsCl in pyridine. Such transformations are found in "Angew. Chem. Int. Ed. Engl.", 33:599 (1994).

Aziridine 24 is then reacted with ROH, RNH₂, RSH or an organometallic (metal-R) to give the corresponding ring opened derivatives 25, 26, 27 and 27.1 respectively. Aziridine openings of this type are found in "Tetrahedron Lett.", 23:5021 (1982) and "Angew. Chem. Int. Ed. Engl.", 33:599 (1994).

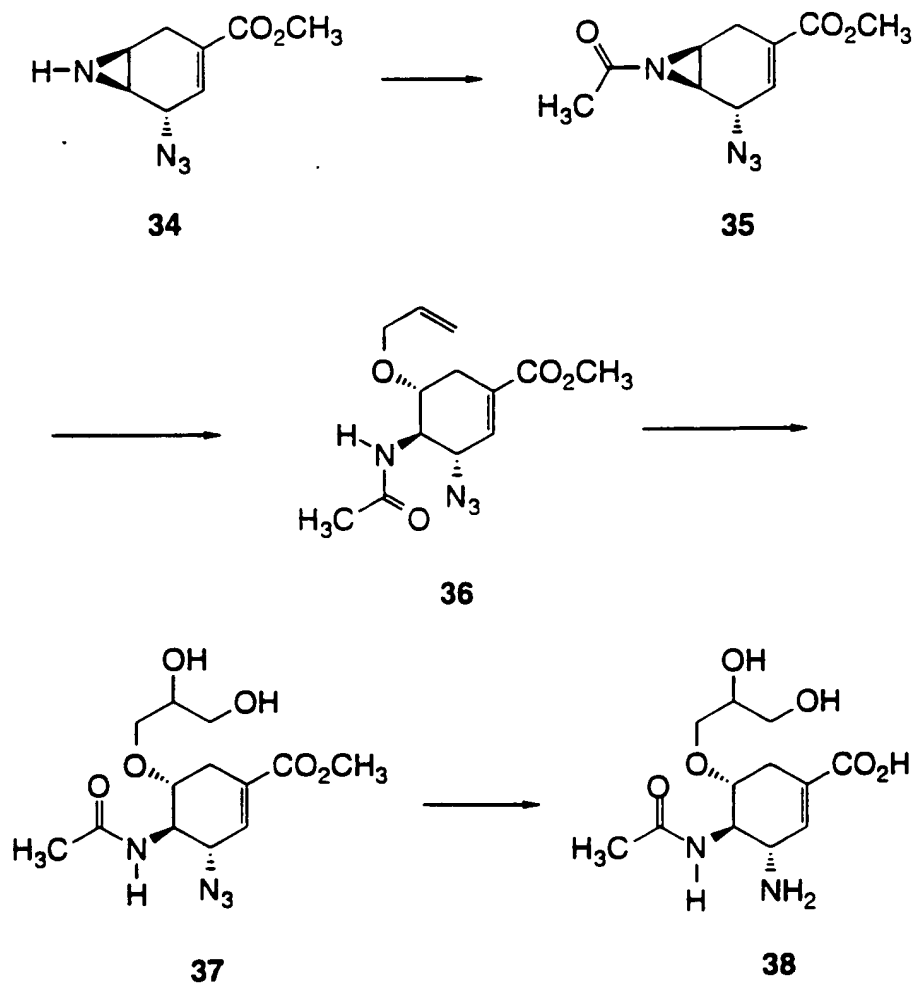
Scheme 5

Another class of compounds of the invention are prepared by the method of Schemes 5a and 5b. Quinic acid is converted to 28 by the method of Shing, T.K.M.; et al.; "Tetrahedron", 47(26):4571 (1991). Mesylation with MsCl in TEA/CH₂Cl₂ will give 29 which is reacted with NaN₃ in DMF to give 30. Reaction of 30 with TFA in CH₂Cl₂ will give 31 which is mesylated with MsCl in TEA/CH₂Cl₂ to give 32. Reaction with triphenylphosphine in water will give 33 which is converted to 35 by sequential application of: 1) CH₃C(O)Cl in pyridine, 2) NaN₃ in DMF, and 3) NaH in THF. Alkylation of 35 with a wide variety of nucleophiles common in the art will provide a number of compounds such as 36. Methods for elaboration of the compounds such as 36 to other embodiments of the invention will be similar to those described above.

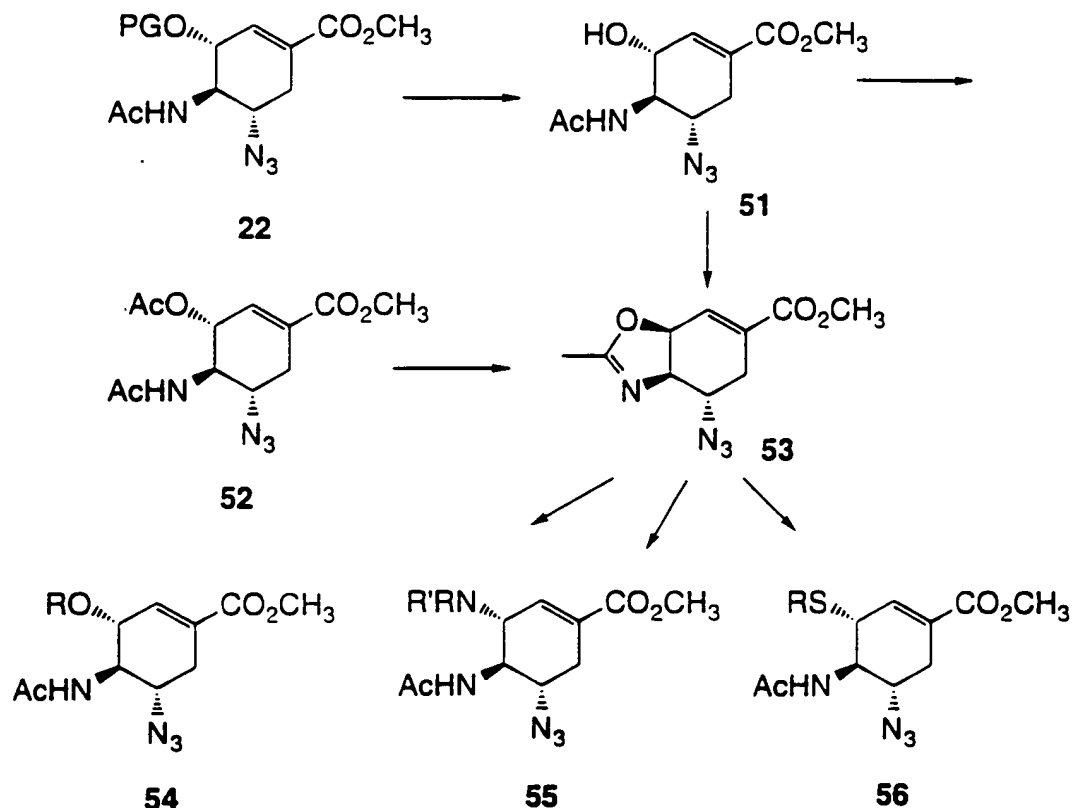
Scheme 5a



Scheme 5b



Scheme 6



Scheme 6

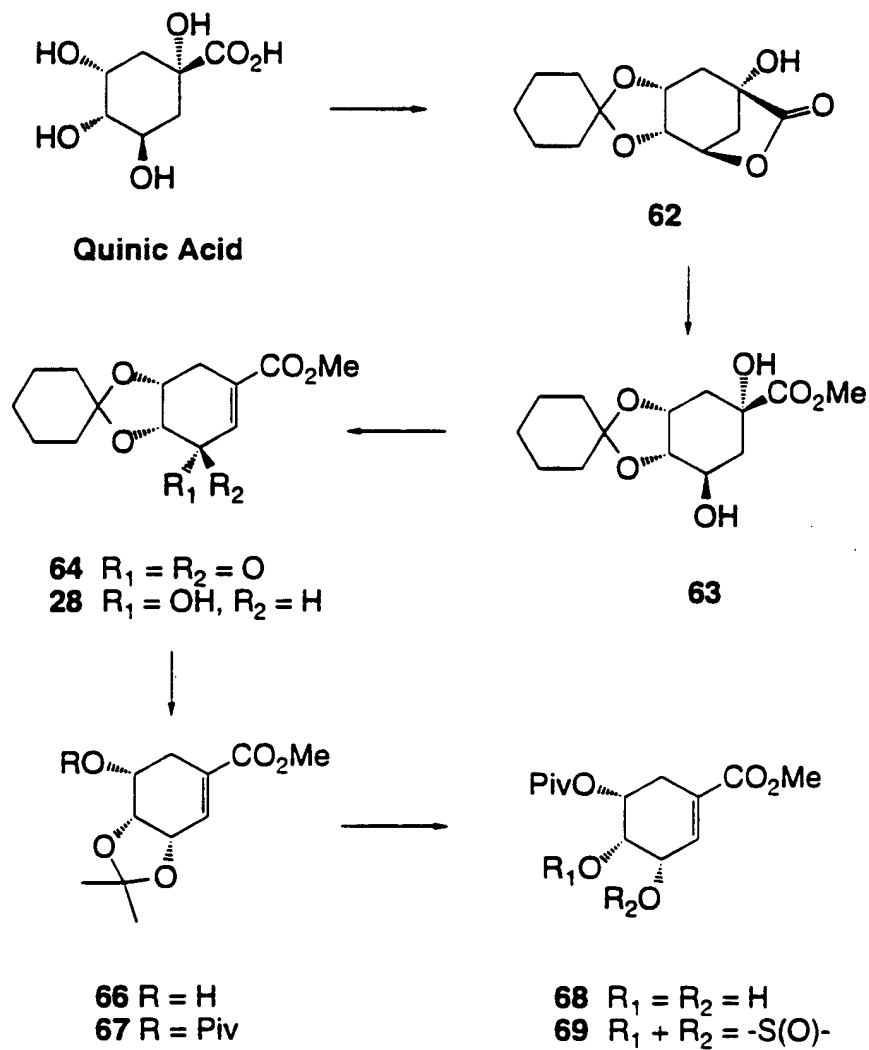
- 5 Another class of compounds of the invention are prepared by the method of Scheme 6. Protected alcohol 22 (PG=methoxymethyl ether) is deprotected under standard conditions described in "Protective Groups in Organic Synthesis" 2nd ed., T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, NY, 1991. Alcohol 51 is converted to acetate 52 with acetic anhydride and pyridine under standard conditions. Acetate 52 is treated with
- 10 TMSOTf or BF₃•OEt to afford oxazoline 53. Such transformations are described in "Liebigs Ann. Chem.", 129 (1991) and "Carbohydrate Research", 181 (1993), respectively. Alternatively, alcohol 51 is transformed to oxazoline 53 by conversion to the corresponding mesylate or tosylate 23 and
- 15 subsequently cyclized to the oxazoline under standard conditions, as described in "J. Org. Chem.", 50:1126 (1985) and "J. Chem. Soc.", 1385 (1970). Oxazoline 53 is reacted with ROH, RR'NH, or RSH (wherein R and R' are selected to be consistent with the definition of W₆ above) provide the corresponding ring opened derivatives 54, 55, and 56 respectively. Such transformations are
- 20 described in "J. Org. Chem.", 49:4889 (1984) and "Chem. Rev.", 71:483 (1971).

Schemes 7-35

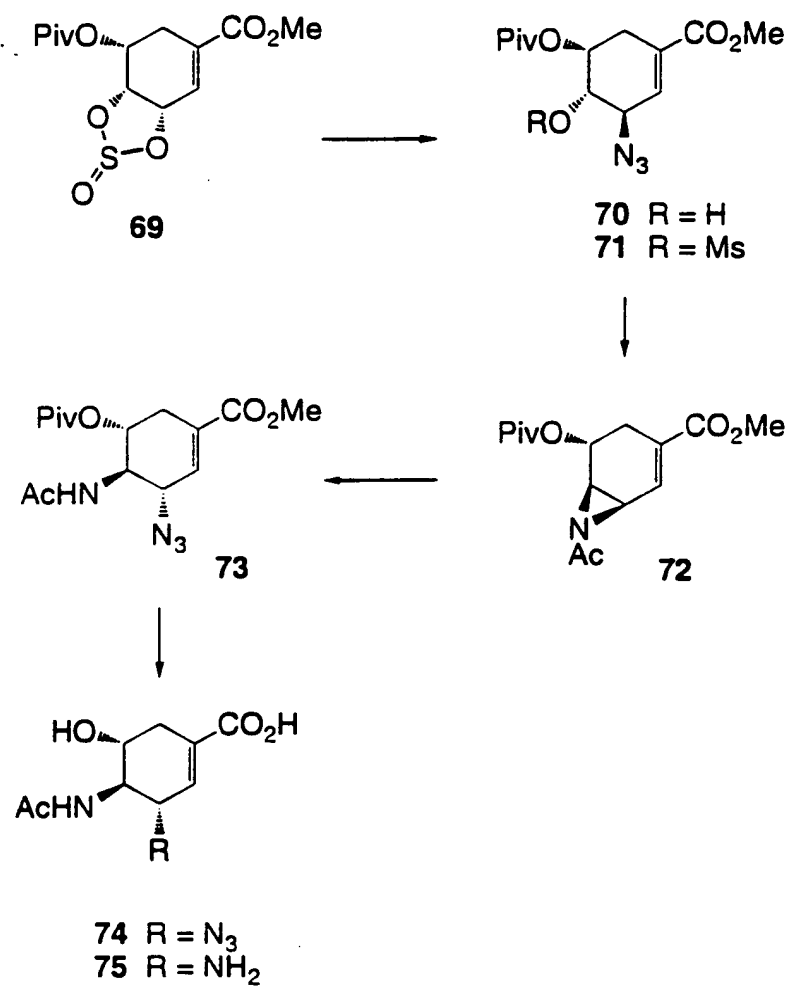
Other exemplary methods of preparing the compounds of the invention are shown in Schemes 7-35 below. A detailed description of the methods is found in the Experimental section below.

5

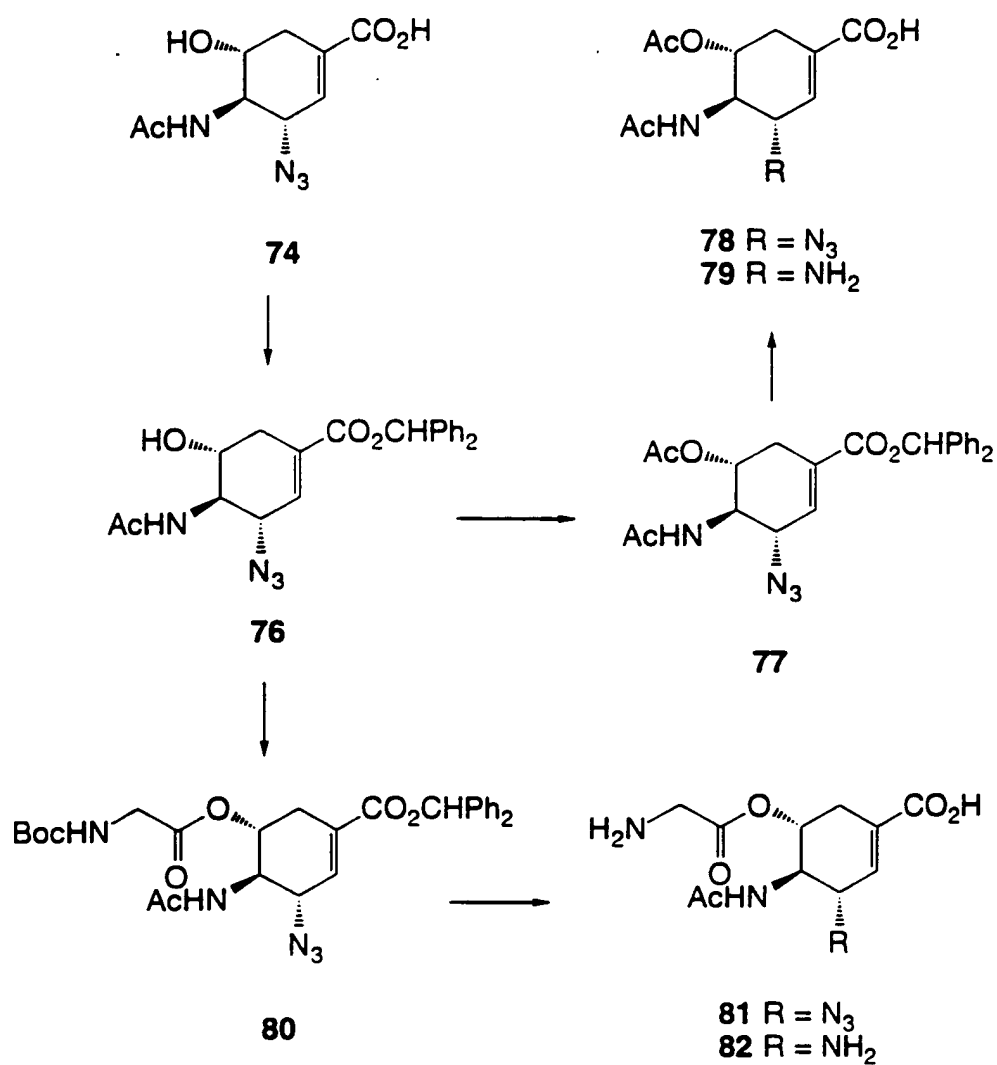
Scheme 7a



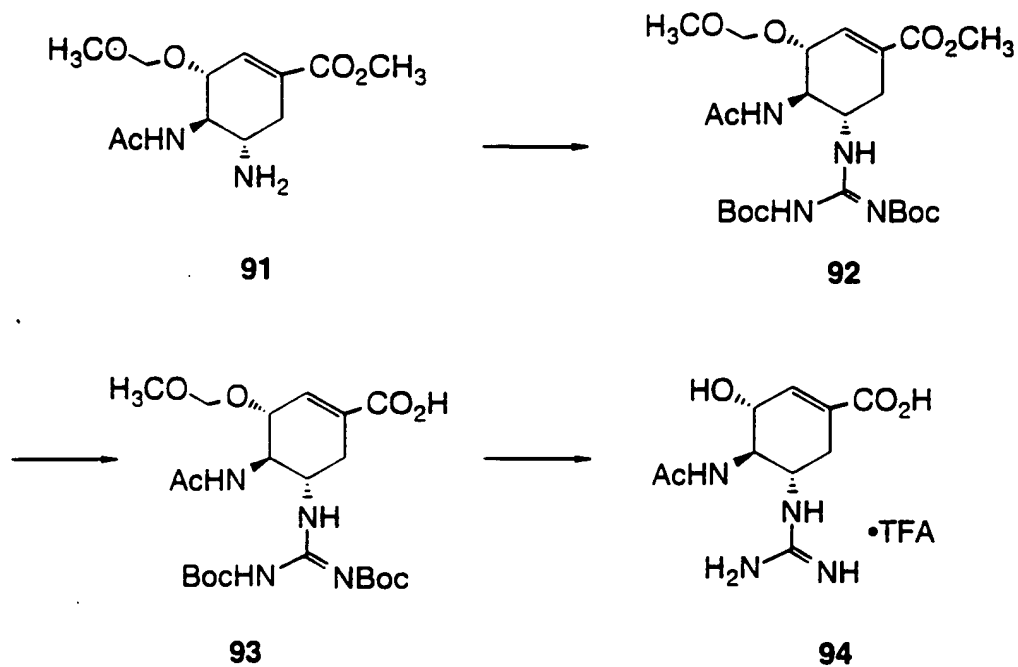
Scheme 7b



Scheme 7c



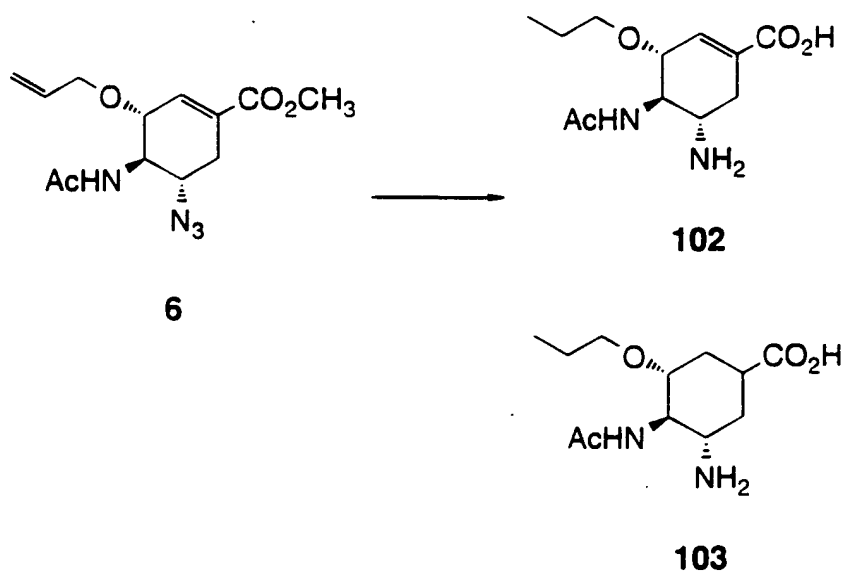
Scheme 8



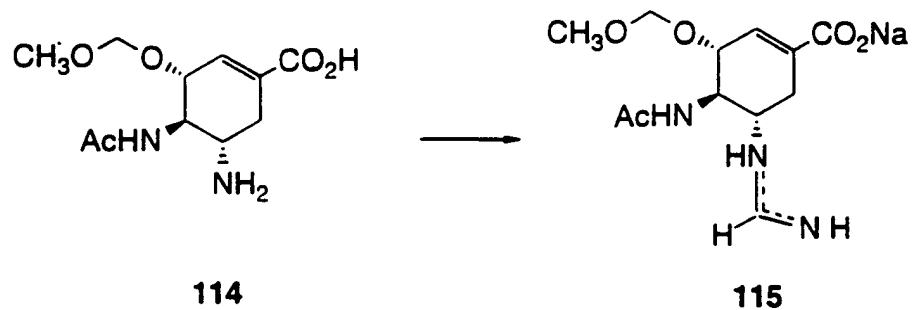
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Scheme 9

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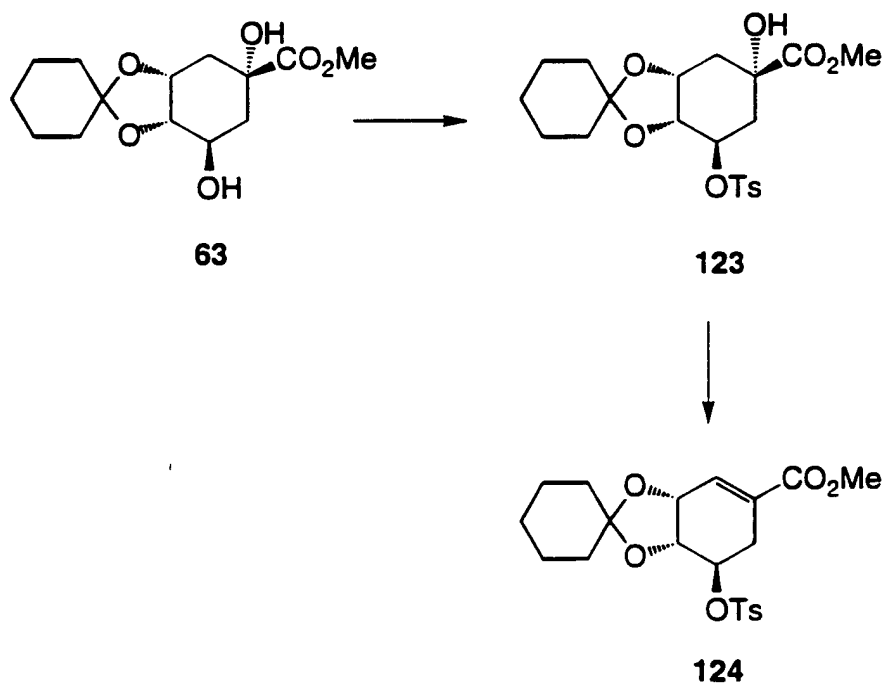


Scheme 10

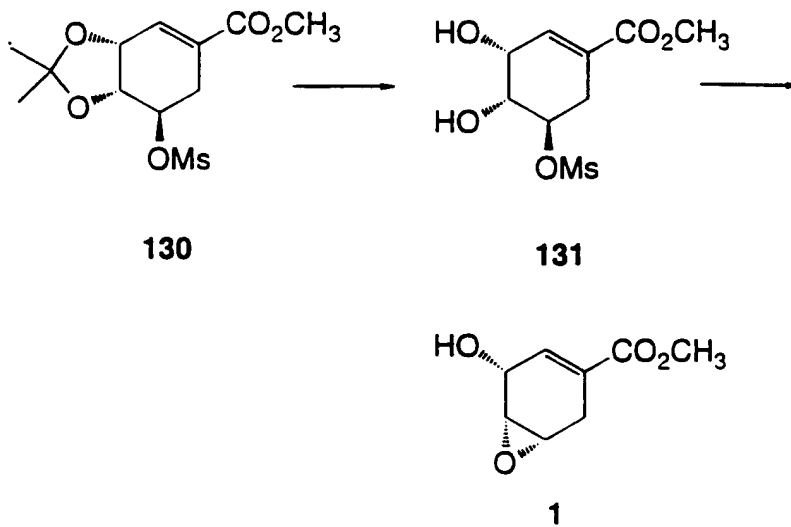


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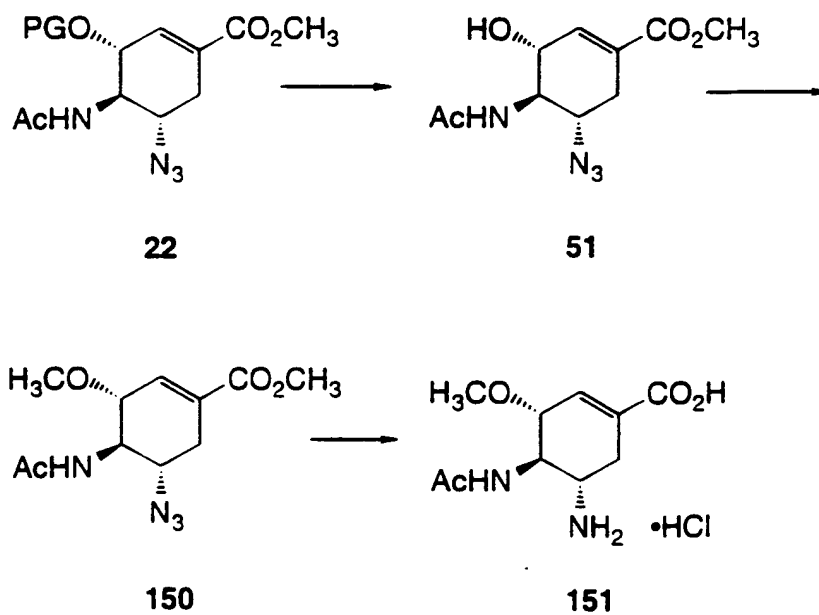
Scheme 11



Scheme 12

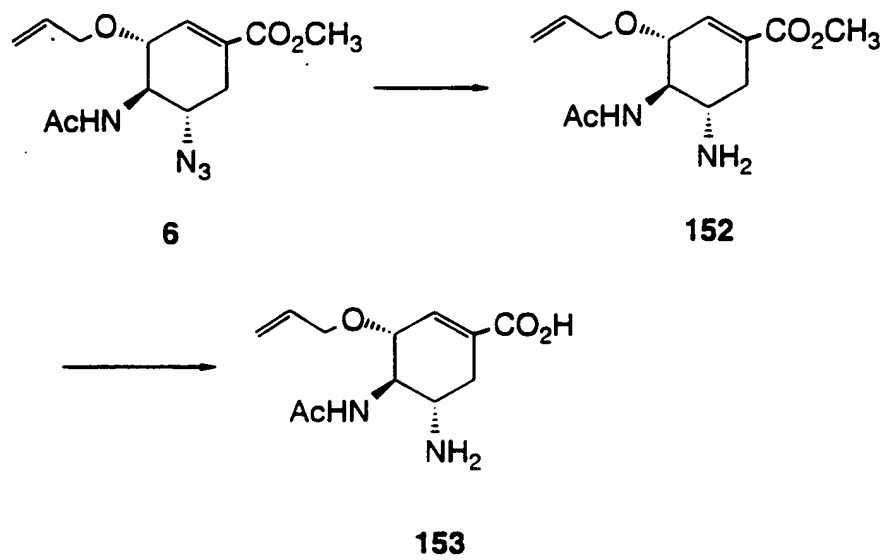


Scheme 13

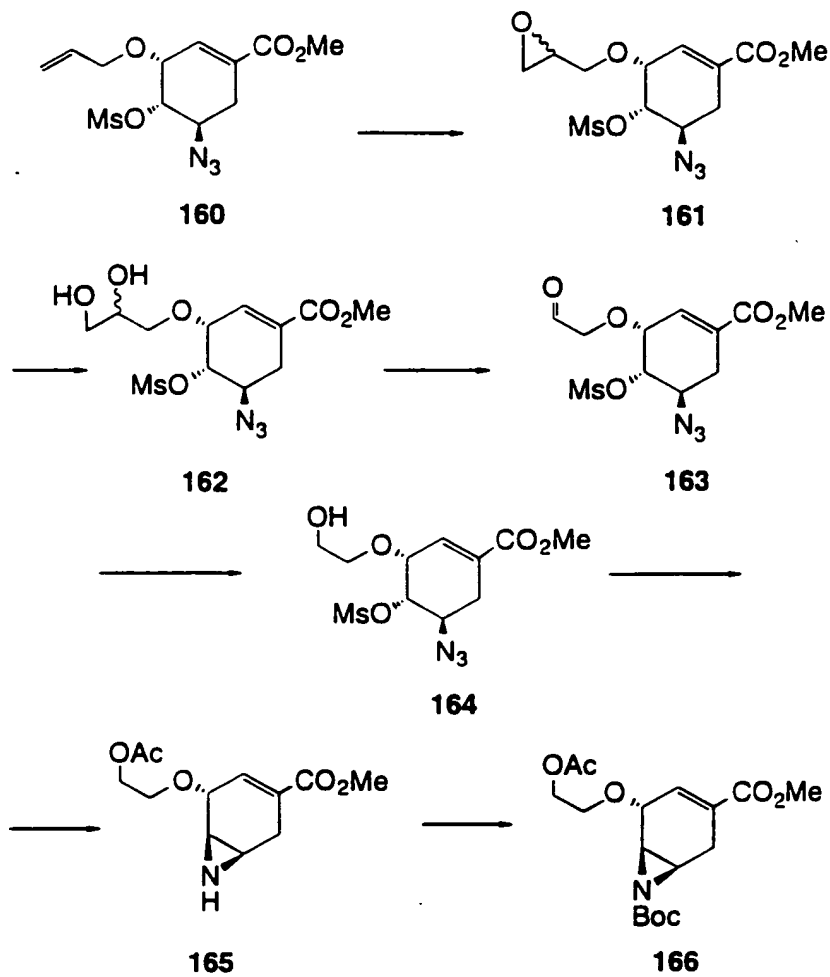


Scheme 14

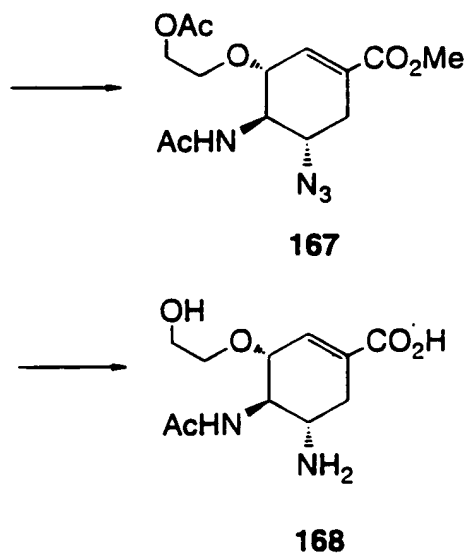
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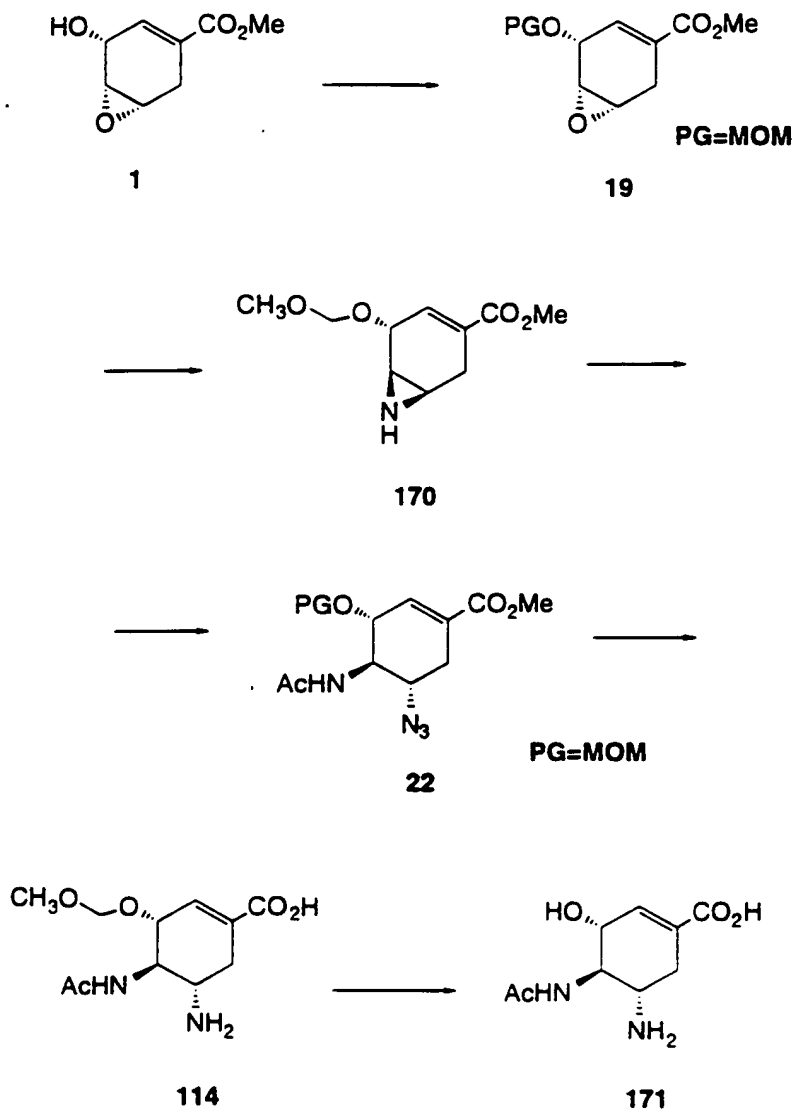
Scheme 15a



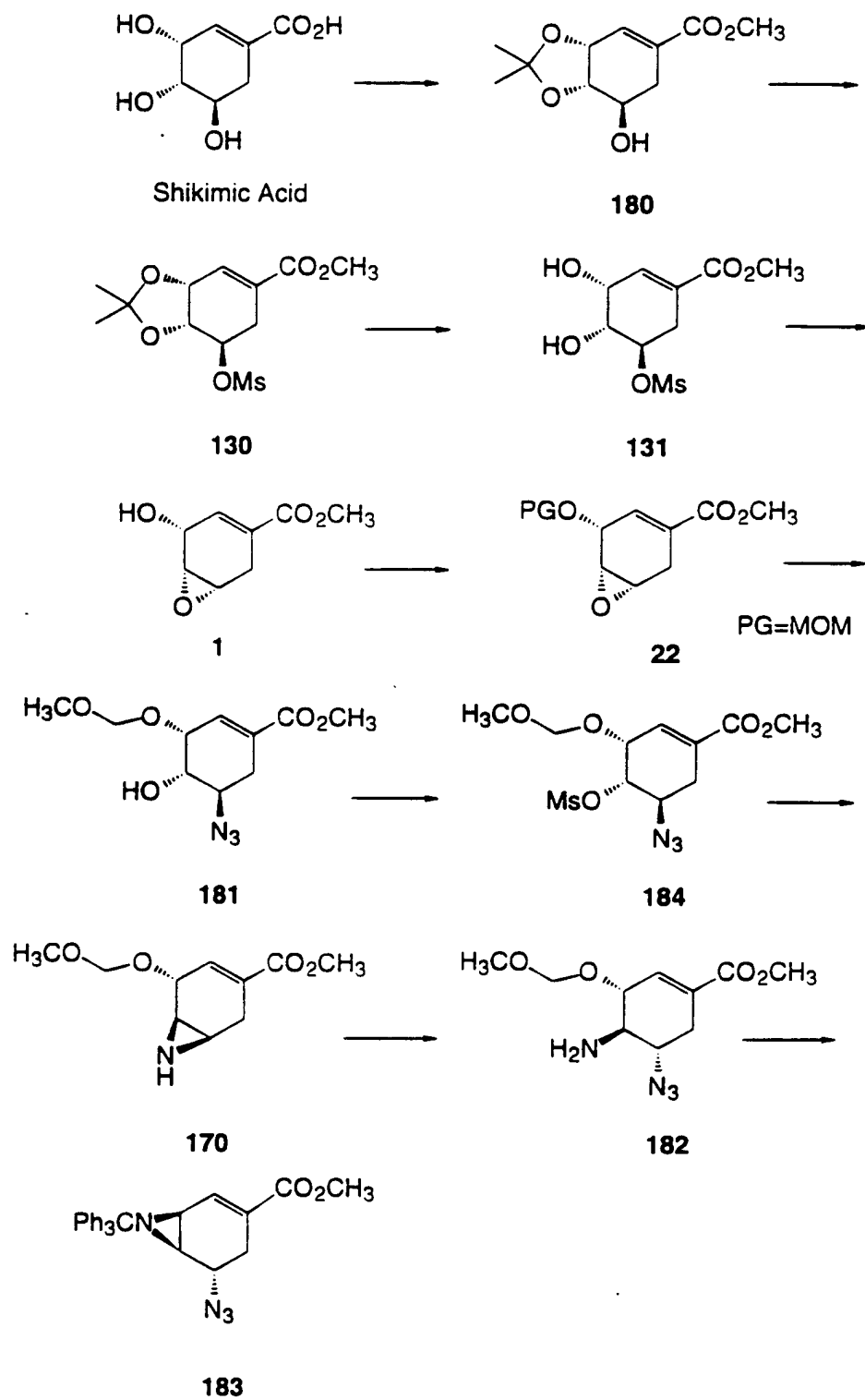
5 Scheme 15b



Scheme 16

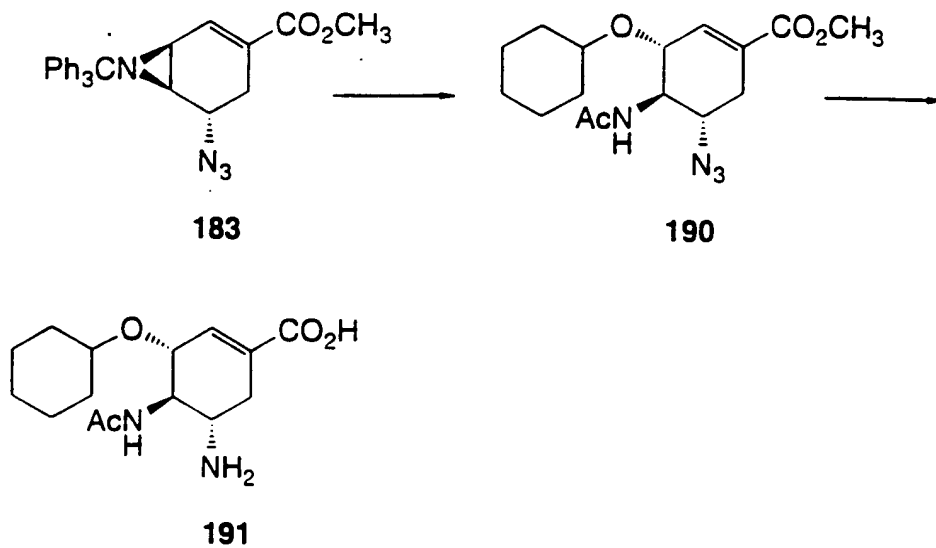


Scheme 17

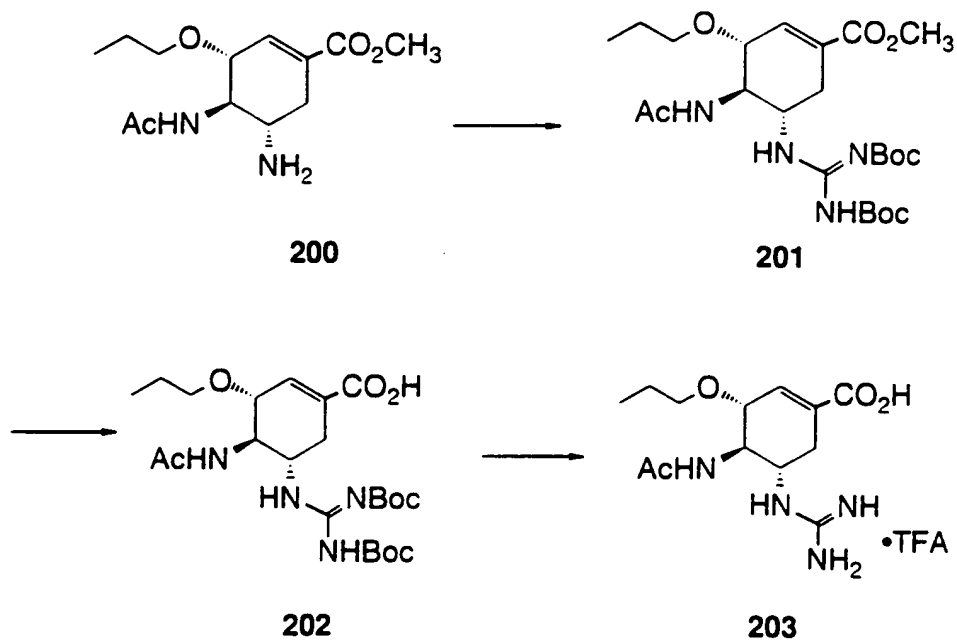


Scheme 18

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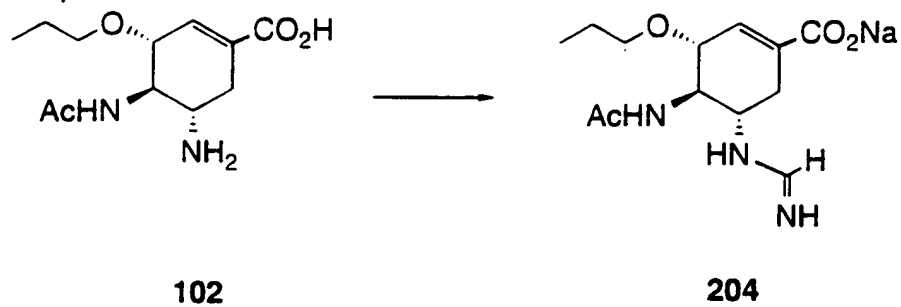


10 Scheme 19



Scheme 20

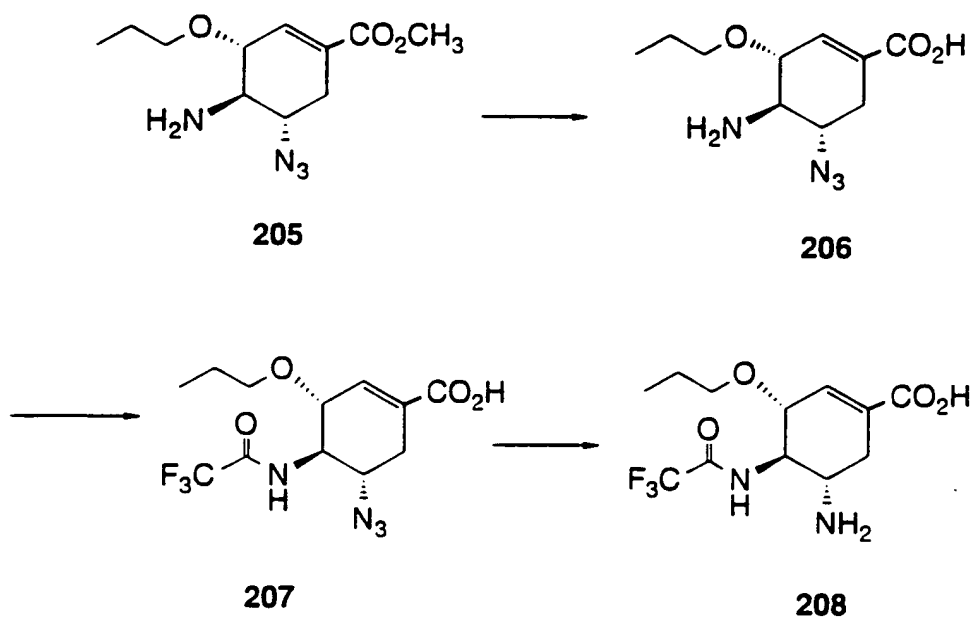
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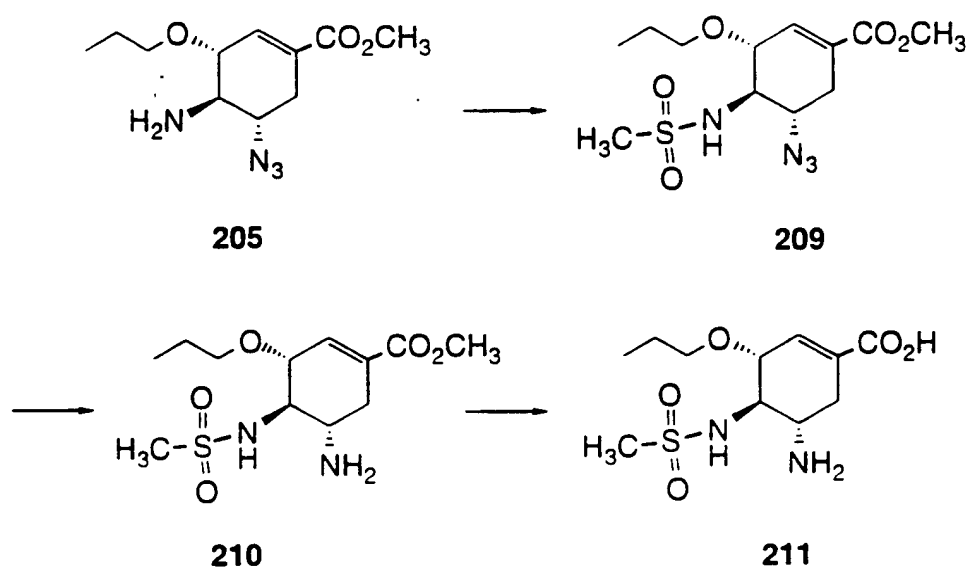
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Scheme 21

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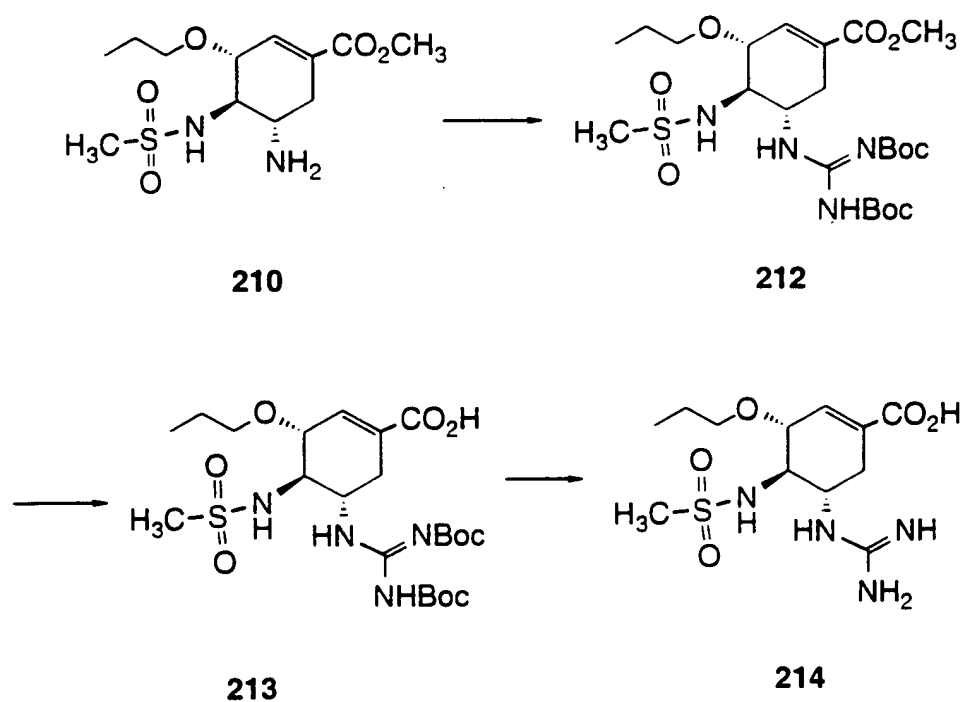


Scheme 22

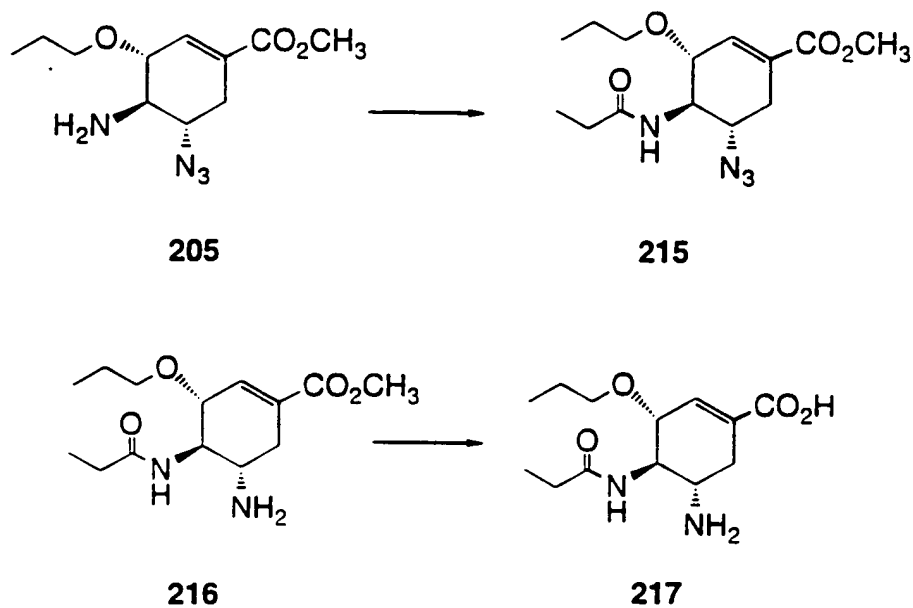


Scheme 23

10



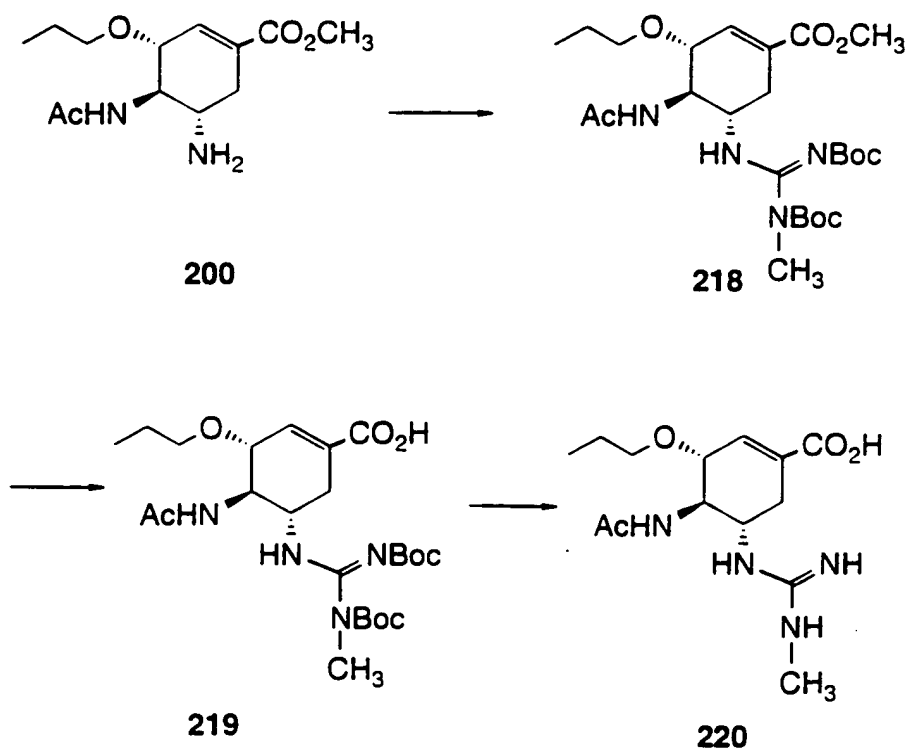
Scheme 24



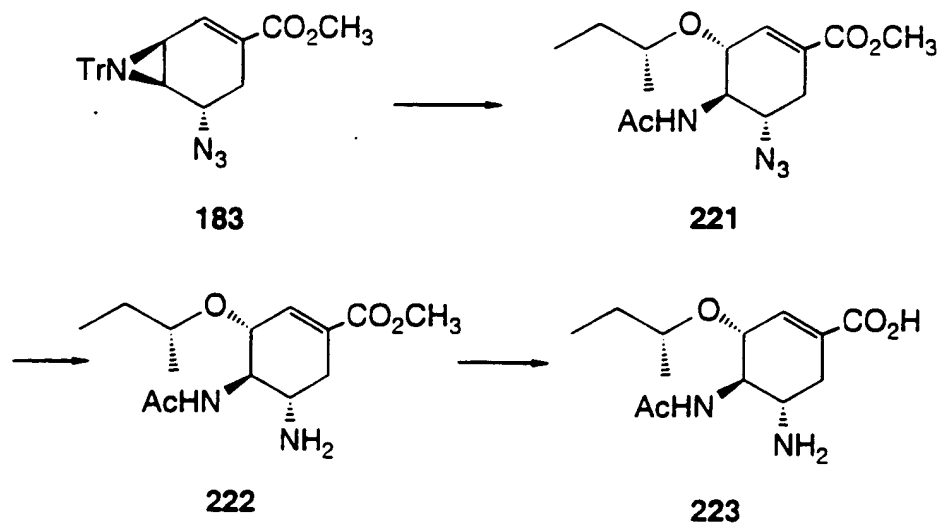
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Scheme 25

10



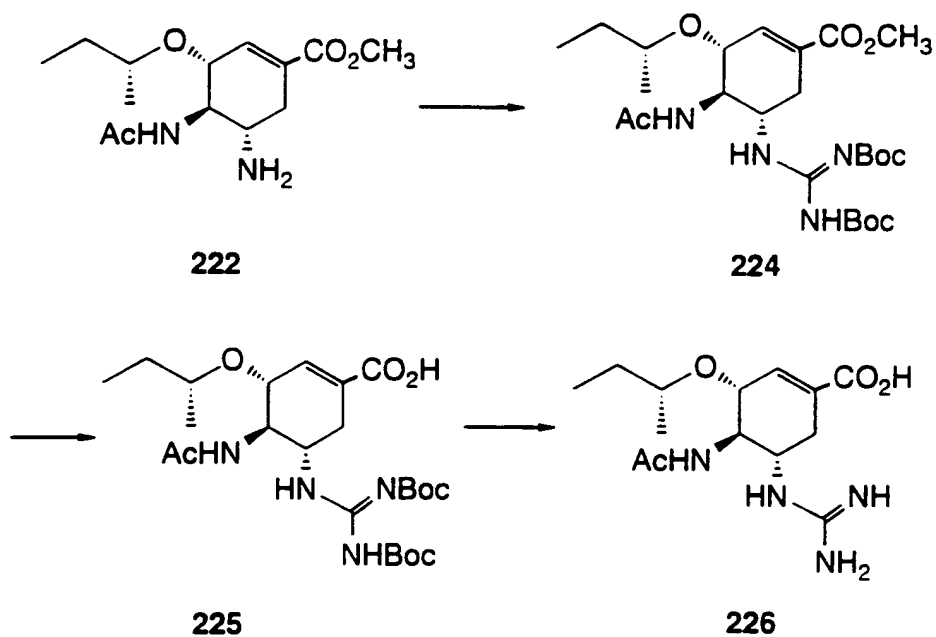
Scheme 26



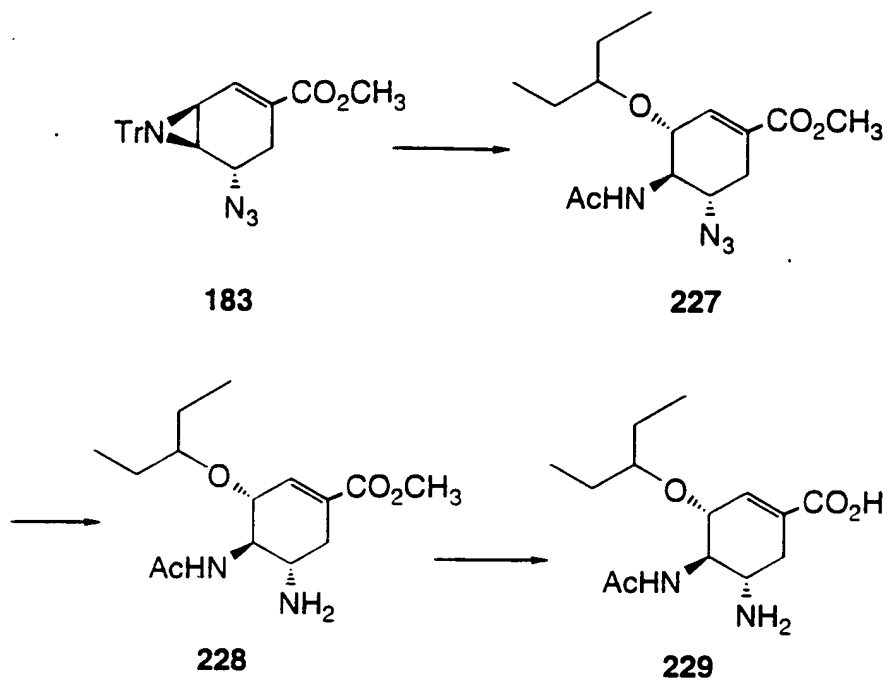
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Scheme 27

10



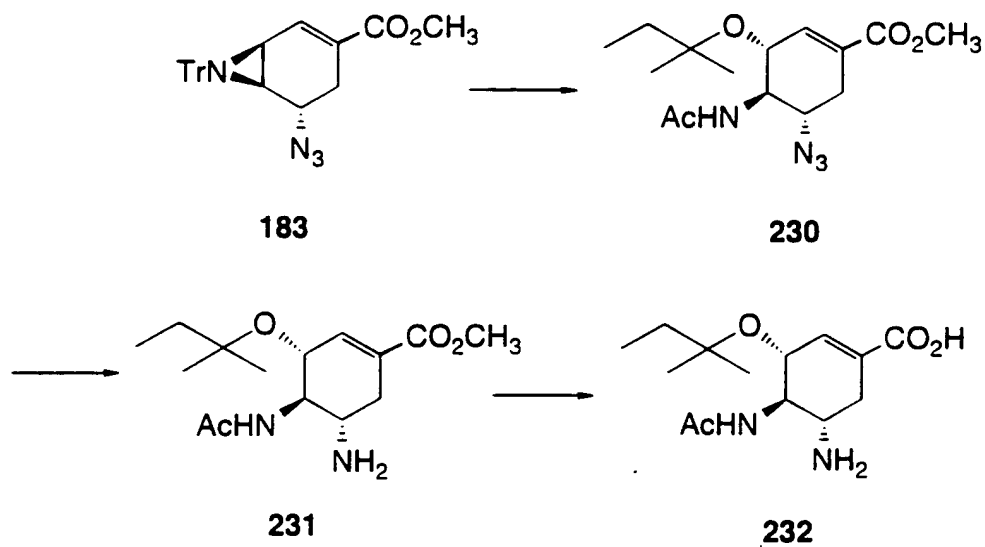
Scheme 28



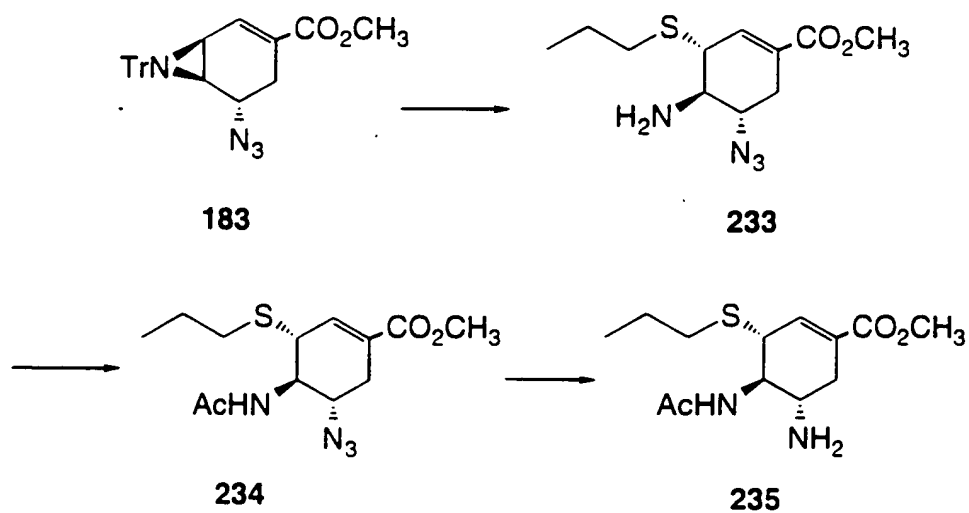
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Scheme 29

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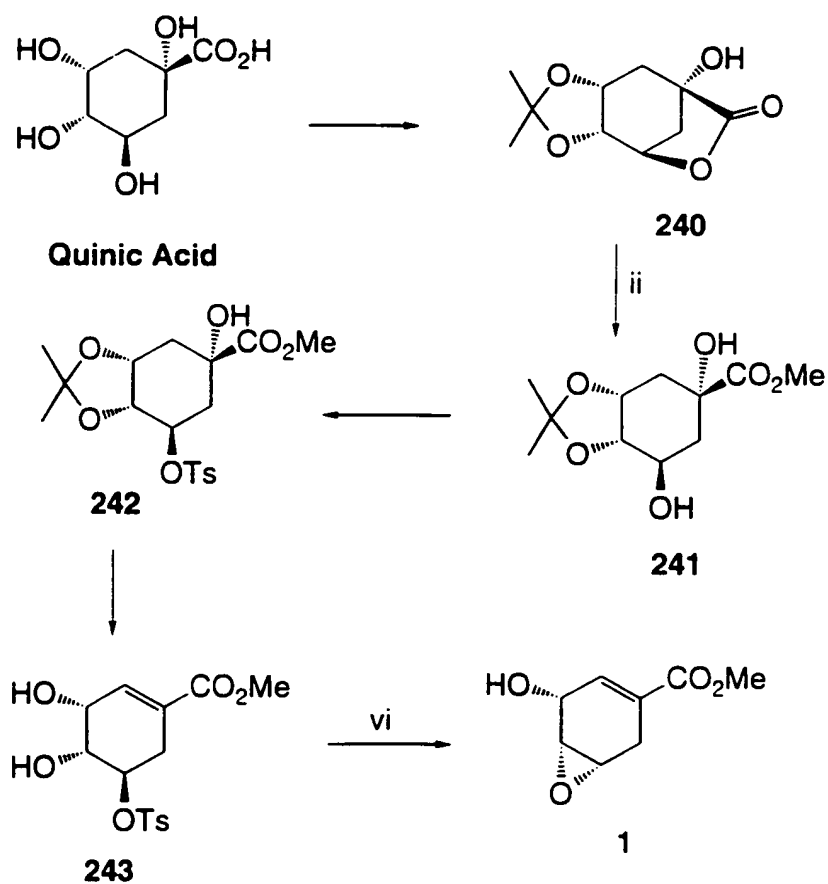


Scheme 30

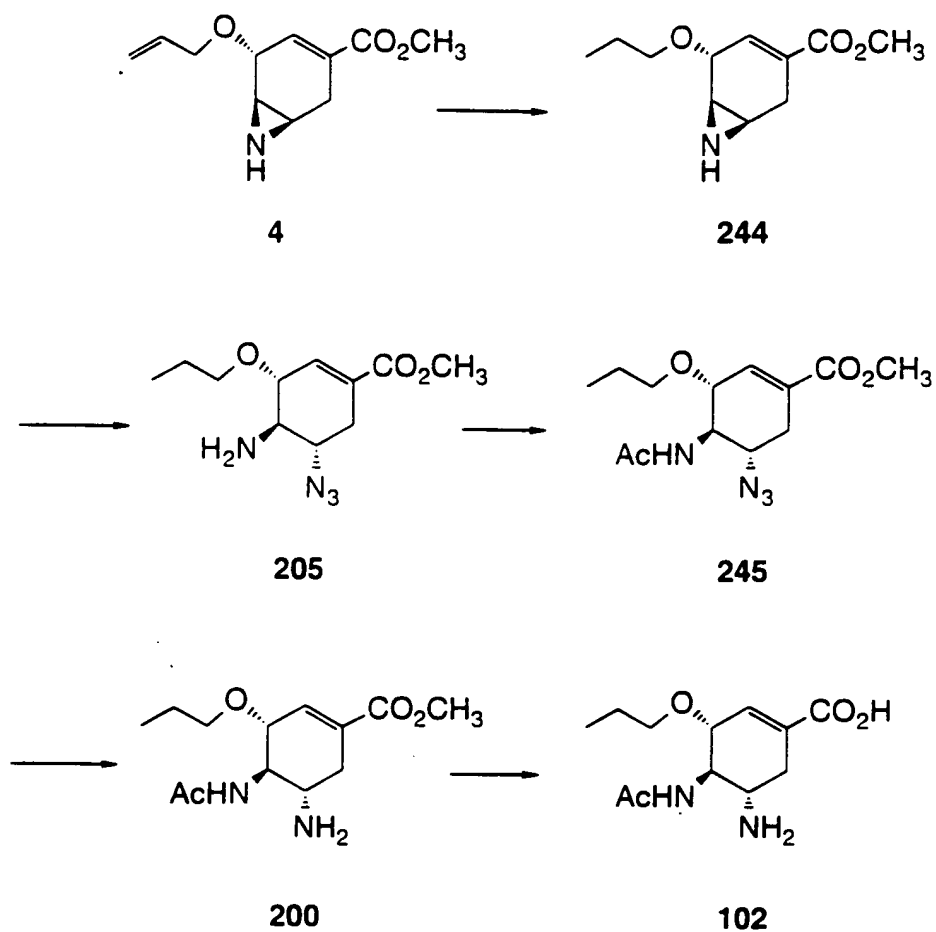


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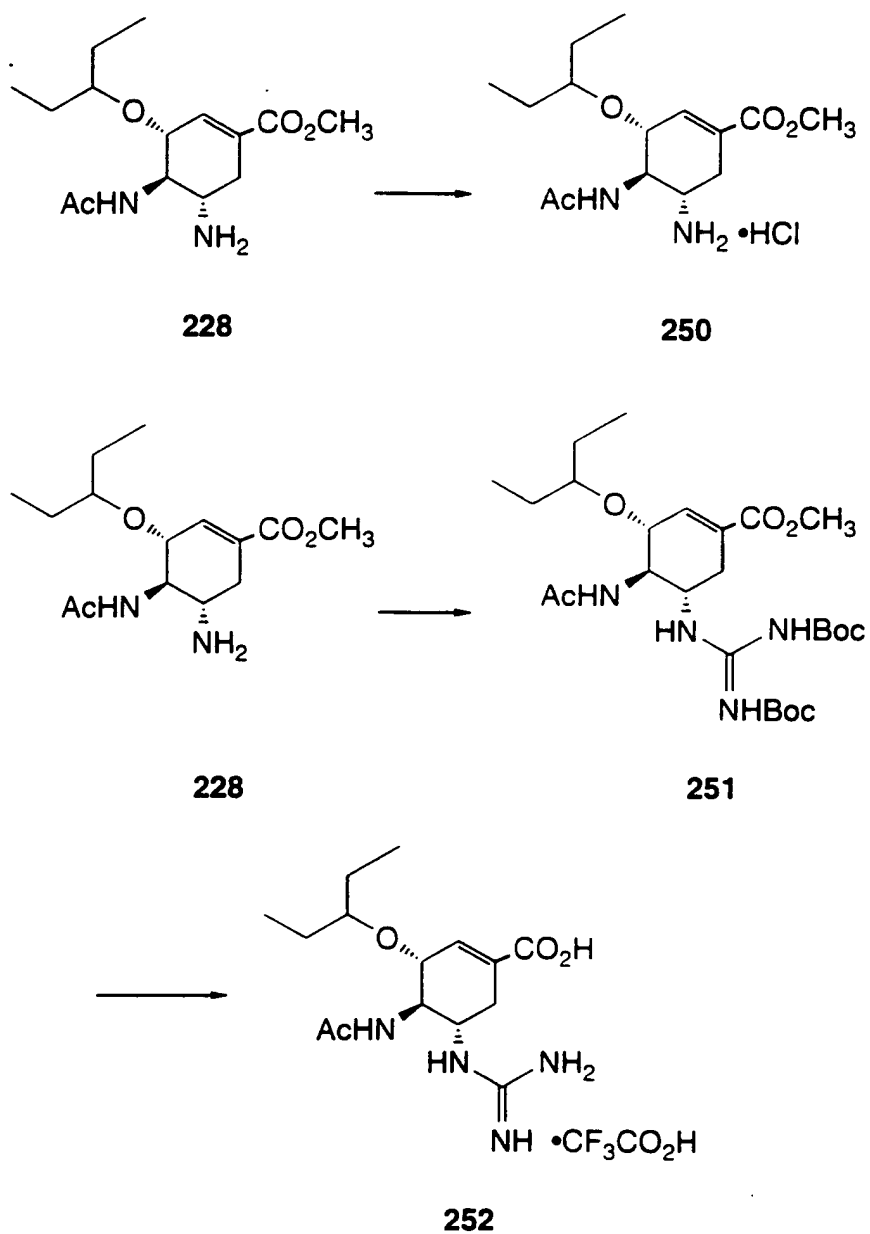
Scheme 31



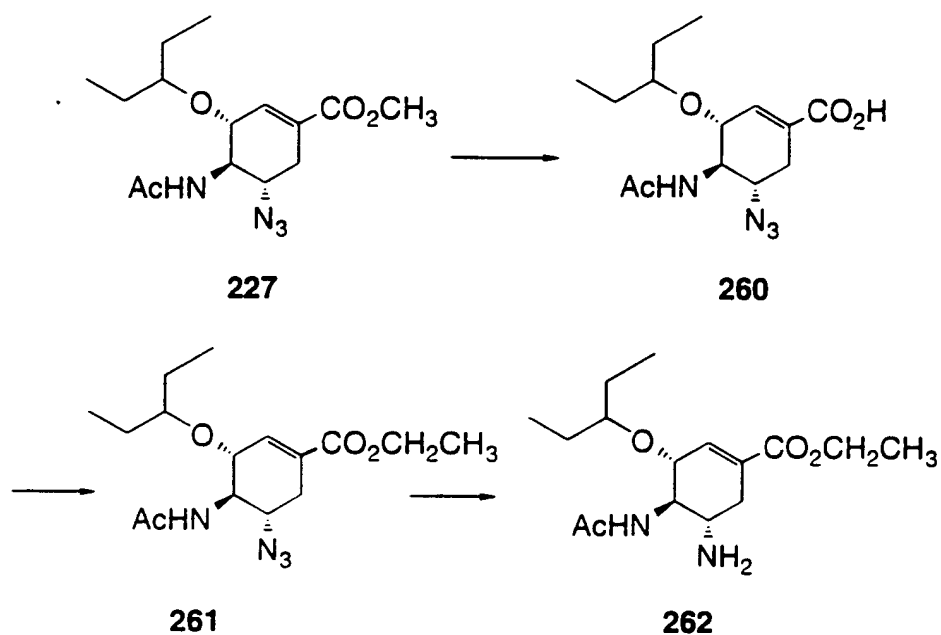
Scheme 32



Scheme 33

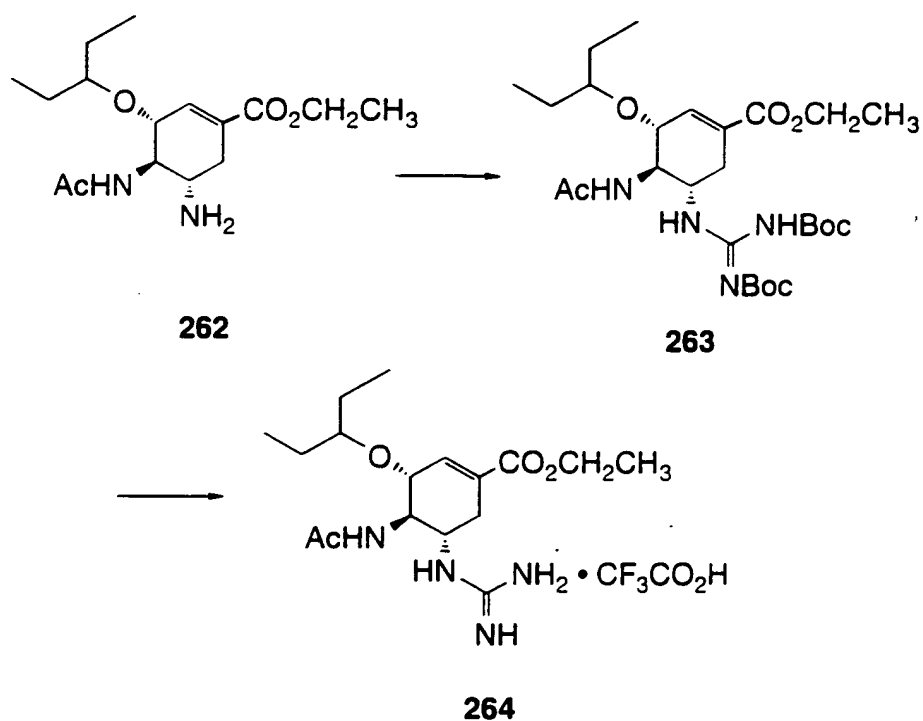


Scheme 34



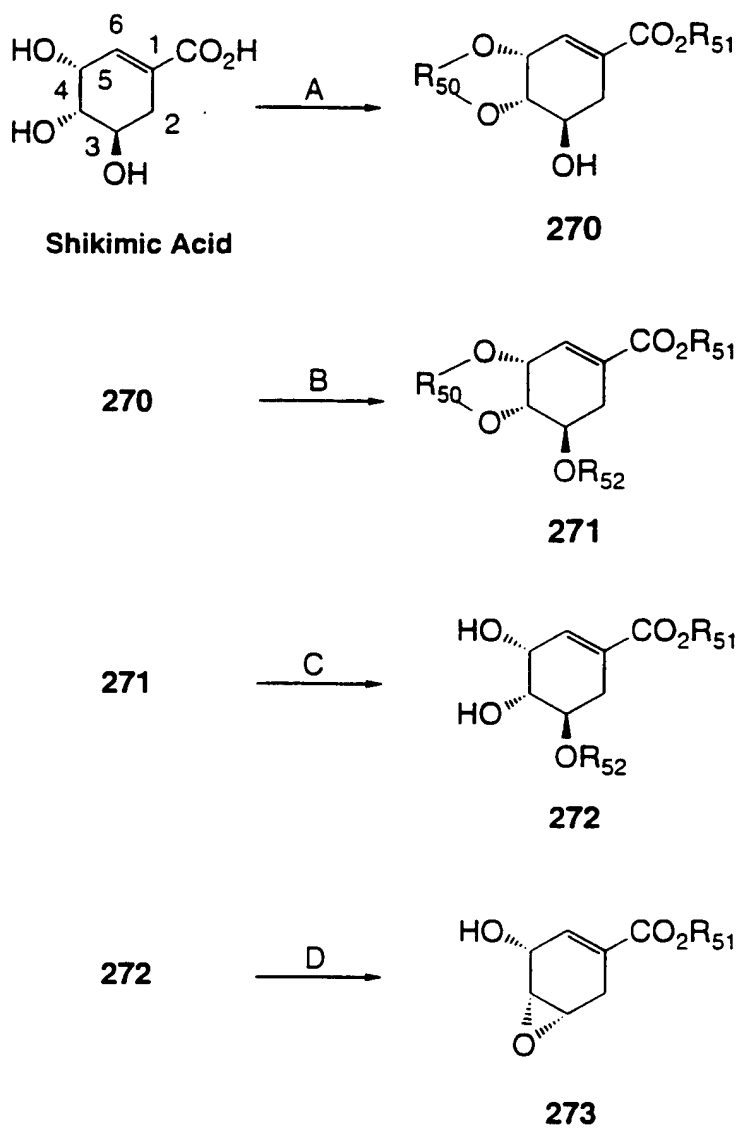
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Scheme 35

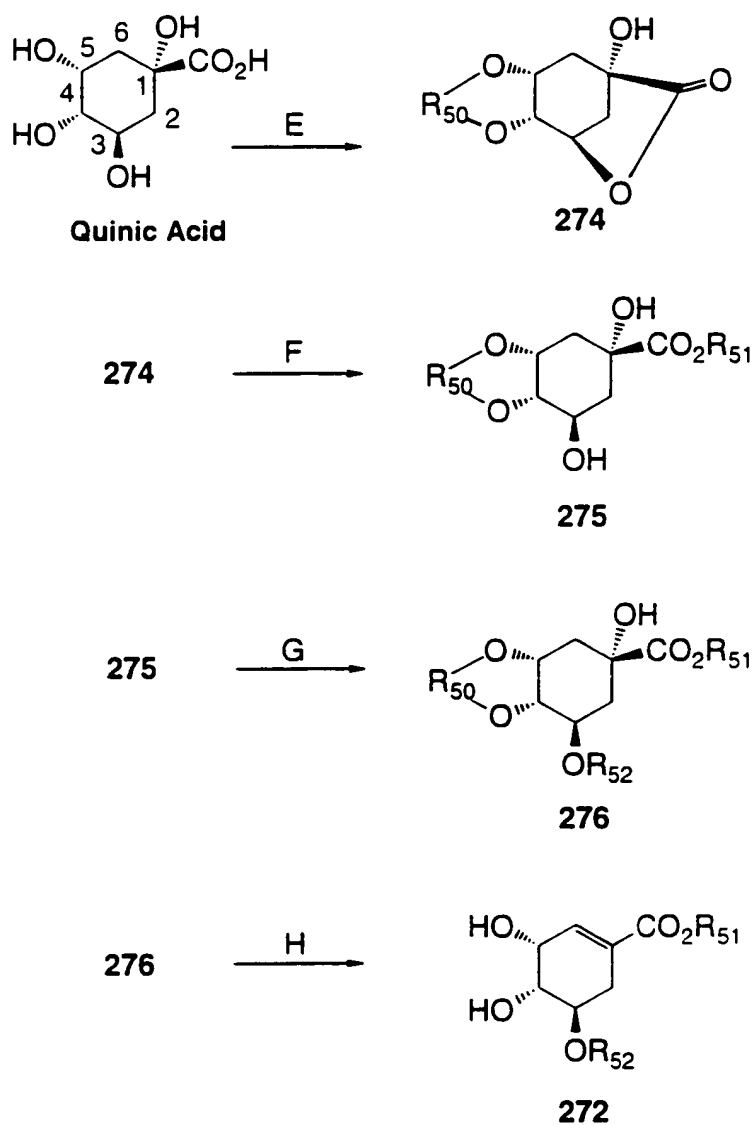


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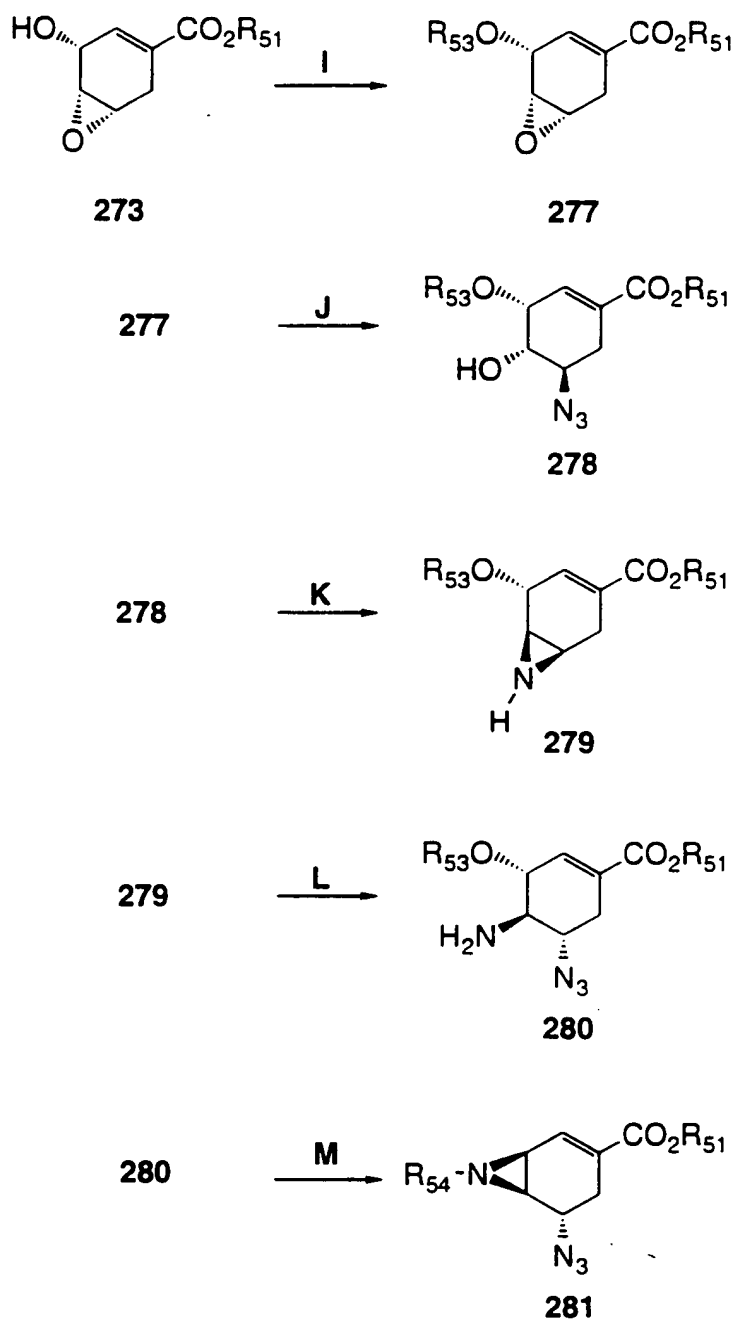
Scheme 36



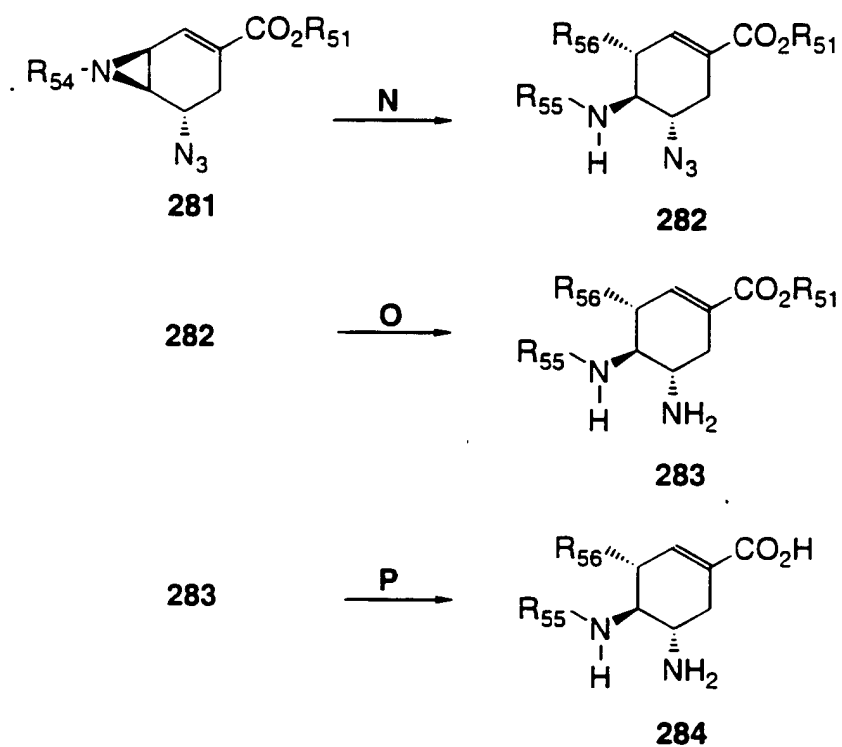
Scheme 37



Scheme 38

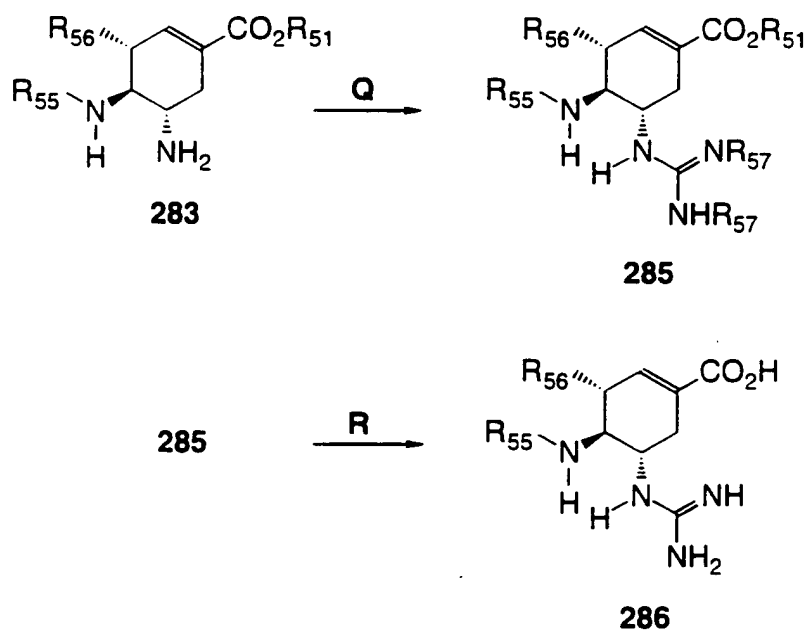


Scheme 39

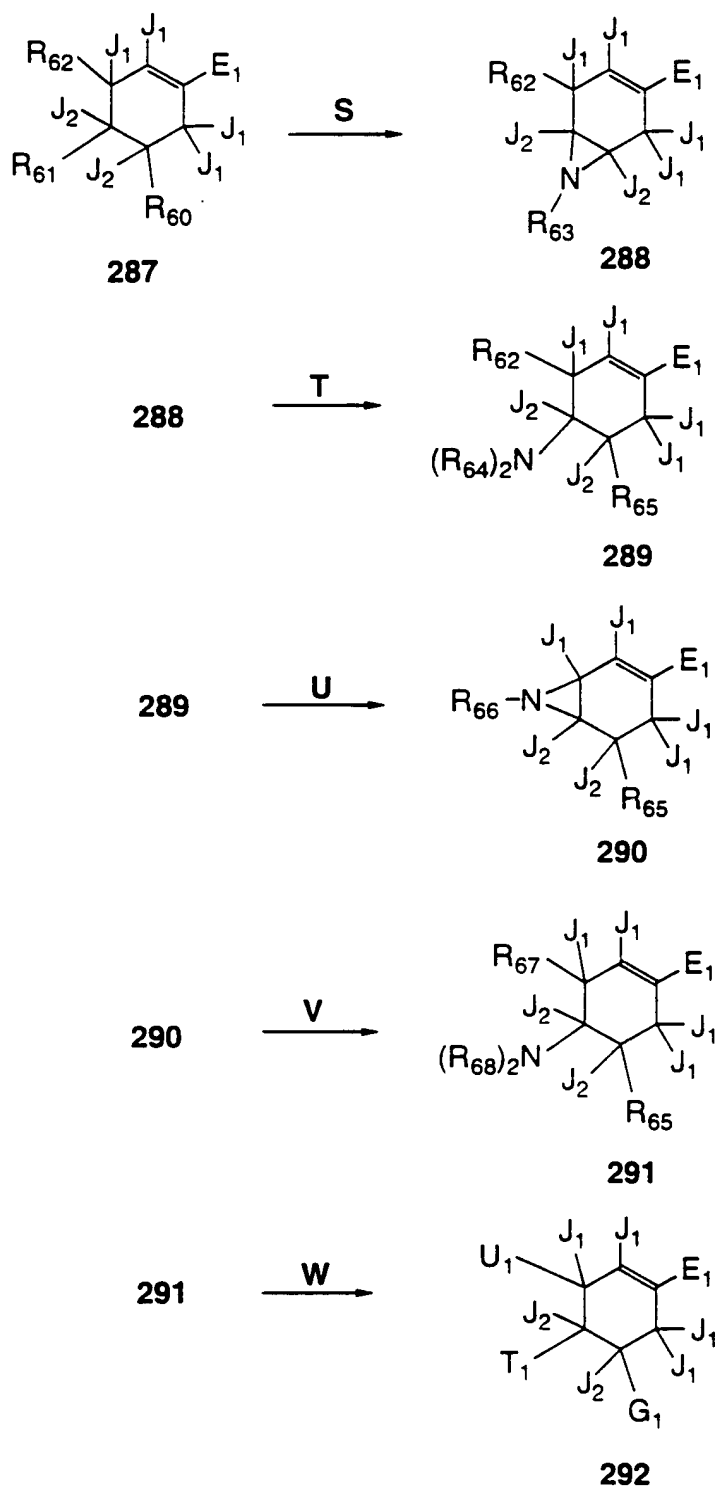


5

Scheme 40



Scheme 40.1



Additional embodiments of methods of making and using compositions of the invention are depicted in **Schemes 36-40.1**. One aspect of the invention is directed to methods of making compounds of the invention comprising processes A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, U, V
5 or W of **Schemes 36-40.1**, alone or in combination with each other. **Table 27** describes exemplary method embodiments of processes A-W. Each embodiment is an individual method using the unit processes A-W alone or in combination. Each method embodiment of **Table 27** is separated by a ";". If the embodiment is a single letter than it corresponds to one of the processes
10 A-W. If it is more than one letter than it corresponds to each of the processes performed sequentially in the order indicated.

Other aspects of the invention are directed to methods of using shikimic acid to prepare compound 270 shown as A in **Schemes 36**, methods of using compound 270 to prepare compound 271 shown as B in **Schemes 36**,
15 methods of using compound 271 to prepare compound 272 shown as C in **Schemes 36**, methods of using compound 272 to prepare compound 273 shown as D in **Schemes 36**, methods of using quinic acid to prepare compound 274 shown as E in **Schemes 37**, methods of using compound 274 to prepare compound 275 shown as F in **Schemes 37**, methods of using
20 compound 275 to prepare compound 276 shown as G in **Schemes 37**, methods of using compound 276 to prepare compound 272 shown as H in **Schemes 37**, methods of using compound 273 to prepare compound 277 shown as I in **Schemes 38**, methods of using compound 277 to prepare compound 278 shown as J in **Schemes 38**, methods of using compound 278 to prepare
25 compound 279 shown as K in **Schemes 38**, methods of using compound 279 to prepare compound 280 shown as L in **Schemes 38**, methods of using compound 280 to prepare compound 281 shown as M in **Schemes 38**, methods of using compound 281 to prepare compound 282 shown as N in **Schemes 39**, methods of using compound 282 to prepare compound 283 shown as O in
30 **Schemes 39**, methods of using compound 283 to prepare compound 284 shown as P in **Schemes 39**, methods of using compound 283 to prepare compound 285 shown as Q in **Schemes 40**, methods of using compound 285 to prepare compound 286 shown as R in **Schemes 40**, methods of using compound 287 to prepare compound 288 shown as S in **Schemes 40.1**,
35 methods of using compound 288 to prepare compound 289 shown as T in **Schemes 40.1**, methods of using compound 289 to prepare compound 290

shown as U in Schemes 40.1, methods of using compound 290 to prepare compound 291 shown as V in Schemes 40.1, and methods of using compound 291 to prepare compound 292 shown as W in Schemes 40.1.

5 General aspects of these exemplary methods are described below and in the Example. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is
10 treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic
15 synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C,
20 more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are
25 used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

30

Process A. Scheme 36

Shikimic acid is used to prepare compound 270 by the following process.

35 The cis-4,5-diol function of shikimic acid is differentiated from the carboxylic acid at carbon 1 by selective protection of these two functionalities.

Typically the cis-4,5-diol function is protected as a cyclic ketal and the carboxylic acid function is protected as an ester.

5 R50 is an acid labile 1,2-diol protecting group such as those described in the above cited work of Greene, typically a cyclic ketal or acetal, more typically, a ketal of cyclohexanone or acetone. R51 is an acid stable carboxylic acid
10 protecting group such as those described in the above cited work of Greene, typically a linear, branched or cyclic alkyl, alkenyl, or alkynyl of 1 to 12 carbon atoms such as those shown as groups 2-7, 9-10, 15, or 100-660 of Table 2, more typically a linear or branched alkyl of 1 to 8 carbon atoms such as those shown
15 as groups 2-5, 9, or 100-358 of Table 2, still more typically a linear or branched alkyl of 1 to 6 carbon atoms such as those shown as groups 2-5, 9, or 100-141 of Table 2, more typically yet, R51 is methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl, or t-butyl.

Shikimic acid is reacted to protect the carboxylic acid with group R51
15 and the cis-4,5-diol with group R50. Typically shikimic acid is treated with an alcohol, such as methanol, ethanol, n-propanol, or i-propanol, and an acid catalyst, such as a mineral acid or a sulfonic acid such as methane, benzene or toluene sulfonic acid, followed by a dialkyl ketal or acetal of a ketone or
20 aldehyde, such as 2,2-dimethoxy-propane, or 1,1-dimethoxy-cyclohexane, in the presence of the corresponding ketone or aldehyde, such as acetone or cyclohexanone. Optionally, the product of the alcohol and acid catalyst treatment is separated, isolated and/or purified prior to treatment with dialkyl ketal or acetal. Alternatively shikimic acid is treated with CH_2N_2 .

Typically, the process comprises treating shikimic acid with an alkanol
25 and a sulfonic acid followed by treating with a geminal-dialkoxyalkane or geminal dialkoxycycloalkane and an alkanone or cycloalkanone to form compound 270. More typically, the process comprises treating shikimic acid with an alkanol and a sulfonic acid; evaporating excess alkanol to form a residue; treating the residue with a geminal-dialkoxyalkane or geminal-
30 dialkoxycycloalkane and an alkanone or cycloalkanone to form compound 270. Still more typically, the process comprises treating shikimic acid with methanol and para-toluenesulfonic acid; evaporating excess methanol to form a residue; treating the residue with 2,2-dimethoxypropane and acetone to form compound 270.

35 An exemplary embodiment of this process is given as Example 55 below.

Process B. Scheme 36

Compound 270 is used to prepare compound 271 by the following process.

5 The hydroxy group at position 3 is activated, typically, activated toward displacement reactions, more typically, activated toward epoxide ring forming displacement with an alcohol at position 4.

10 R52 is an alcohol activating group, typically, an activating group toward displacement reactions, more typically, an activating group toward epoxide ring forming displacement with an alcohol at position 4. Such groups include those typical in the art such as sulfonic acid esters, more typically, methane, benzene or toluene sulfonic acid esters. In one embodiment, R52, taken together with O (i.e. -OR52), is a leaving group such as those common in the art.

15 Typically the process comprises treating compound 270 with an acid halide to form compound 271. More typically, the process comprises treating compound 270 with a sulfonic acid halide in a suitable solvent to form compound 271. Still more typically, the process comprises treating compound 270 with a sulfonic acid halide in a suitable solvent such as an amine, 20 optionally, in the presence of a cosolvent, such as a haloalkane, to form compound 271. More typically yet, the process comprises treating compound 270 with methane sulfonyl chloride in triethylamine/dichloromethane to form compound 271.

25 An exemplary embodiment of this process is given as Example 56 below.

Process C. Scheme 36

Compound 271 is used to prepare compound 272 by the following process.

30 The acid labile protecting group (R50) for the hydroxy groups at positions 4 and 5 is removed. Typically, R50 is removed without substantially removing base labile carboxylic acid protecting groups (e.g. R51) or hydroxy activating groups (e.g. R52). Still more typically, R50 is cleaved under acidic conditions.

35 Typically the process comprises treating compound 271 with a protic solvent, more typically, in the presence of an acid catalyst as described above.

Still more typically, the process comprises treating compound 271 with an alkanol as described above and an acid catalyst as described above. More typically yet, the process comprises treating compound 271 with methanol and para-toluene sulfonic acid to produce compound 272.

- 5 An exemplary embodiment of this process is given as Example 57 below.

Process D, Scheme 36

- 10 Compound 272 is used to prepare compound 273 by the following process.

The activated hydroxy group at position 3 of compound 272 is displaced by the hydroxy at position 4 of compound 272 to produce epoxide compound 273. Typically the displacement is catalyzed by a suitable base, more typically, an amine base such as DBU or DBN.

- 15 Typically the process comprises treating compound 272 with a basic catalyst, optionally in the presence of a suitable solvent. Still more typically, the process comprises treating compound 272 with an amine base in a polar, non-protic solvent such as diethyl ether or THF. More typically yet, the process comprises treating compound 272 with DBU in THF to produce
20 compound 273.

An exemplary embodiment of this process is given as Example 58 below.

Process E, Scheme 37

- 25 Quinic acid is used to prepare compound 274 by the following process. The cis-4,5-diol function of quinic acid is differentiated from the carboxylic acid at carbon 1 by selective protection of these two functionalities. Typically the cis-4,5-diol function is protected as a cyclic ketal and the carboxylic acid function is protected as a lactone with the hydroxy group at position 3.

- 30 R50 is as described above.

- Typically, the process comprises treating quinic acid with a geminal-dialkoxyalkane or geminal dialkoxycycloalkane, as described above, and an alkanone or cycloalkanone, as described above, optionally, in the presence of an acid catalyst, as described above, to form compound 274. More typically,
35 the process comprises treating quinic acid with a geminal-dialkoxyalkane or geminal-dialkoxycycloalkane, an alkanone or cycloalkanone, and an acid

catalyst to form compound 270. Still more typically, the process comprises treating quinic acid with 2,2-dimethoxypropane, acetone, and para-toluenesulfonic acid to form compound 274.

5 An exemplary embodiment of this process is given as Example 101 below.

Process F, Scheme 37

Compound 274 is used to prepare compound 275 by the following process.

10 The lactone is opened to form compound 275. Typically, the lactone is opened to produce a protected carboxylic acid at position 1 and a free hydroxy at position 3. More typically, the lactone is opened under basic conditions to produce an R₅₁ protected carboxylic acid at position 1 and a free hydroxy group at position 3.

15 R₅₁ is as described above.

Typically compound 274 is treated with a suitable base in a suitable protic solvent. More typically compound 275 is treated with a metal alkoxide base, such as sodium, potassium or lithium alkoxide, in an alkanol, as described above. Still more typically, compound 274 is treated with NaOMe in
20 MeOH to produce compound 275.

An exemplary embodiment of this process is given as Example 102 below.

Process G, Scheme 37

25 Compound 275 is used to prepare compound 276 by the following process.

The hydroxy group at position 3 is activated, typically, activated toward displacement reactions, more typically, activated toward epoxide ring forming displacement with an alcohol at position 4.

30 R₅₂ is an alcohol activating group, typically, an activating group toward displacement reactions, more typically, an activating group toward epoxide ring forming displacement with an alcohol at position 4. Such groups include those typical in the art such as sulfonic acid esters, more typically, methane, benzene or toluene sulfonic acid esters. In one embodiment, R₅₂, taken
35 together with O (i.e. -OR₅₂), is a leaving group such as those common in the art.

Typically the process comprises treating compound 275 with an acid halide to form compound 276. More typically, the process comprises treating compound 275 with a sulfonic acid halide in a suitable solvent to form compound 276. Still more typically, the process comprises treating compound 275 with a sulfonic acid halide in a suitable solvent such as an amine, optionally, in the presence of a cosolvent, such as a haloalkane, to form compound 276. More typically yet, the process comprises treating compound 275 with *p*-toluene sulfonyl chloride in pyridine dichloromethane to form compound 276.

An exemplary embodiment of this process is given as Example 103 below.

Process H. Scheme 37

Compound 276 is used to prepare compound 272 by the following process.

The hydroxy group at position 1 is eliminated and the *cis*-4,5-diol protecting group is removed. The hydroxy group at position 1 is eliminated to form an olefinic bond between positions 1 and 6 and the *cis*-4,5-diol protecting group is removed to regenerate the *cis*-4,5-diol.

Typically the process comprises treating compound 276 with a suitable dehydrating agent, such as a mineral acid (HCl, H₂SO₄) or SO₂Cl₂. More typically, compound 276 is treated with SO₂Cl₂, followed by an alkanol, optionally in the presence of an acid catalyst. Still more typically, compound 276 is treated with SO₂Cl₂ in a suitable polar, aprotic solvent, such as an amine to form an olefin; the olefin is treated with an alkanol, as described above, and an acid catalyst, as described above, to form compound 272. More typically yet, compound 276 is treated with SO₂Cl₂ in pyridine/CH₂Cl₂ at a temperature between -100°C and 0°C, typically -100°C and -10°C, more typically -78°C, to form an olefin; the olefin is treated with methanol and para-toluene sulfonic acid to form compound 272.

An exemplary embodiment of this process is given as Example 104 below.

Process I. Scheme 38

Compound 273 is used to prepare compound 277 by the following process.

The hydroxy group at position 5 is protected. Typically the protecting group is an acid labile hydroxy protecting. More typically, the protecting group resists transfer to adjacent hydroxy groups.

5 R53 is an acid labile hydroxy protecting group such as those described in the above cited work of Greene. More typically, R53 is an acid cleavable ether, still more typically, R53 is methoxymethyl (MOM, CH₃-O-CH₂-).

Typically the process comprises treating compound 273 with a hydroxy protecting group reagent as described in Greene. More typically the process comprises treating compound 273 with a substituted or unsubstituted
10 haloalkane or alkene, such as methoxymethyl chloride (MOM chloride, CH₃-O-CH₂-Cl), in a suitable solvent, such as a polar, aprotic solvent. Still more typically, the process comprises treating compound 273 with MOM chloride in an amine solvent. More typically yet, the process comprises treating compound 273 with MOM chloride in diisopropyl ethyl amine.

15 An exemplary embodiment of this process is given as Example 59 below.

Process I, Scheme 38

Compound 277 is used to prepare compound 278 by the following
20 process.

The epoxide at positions 3 and 4 is opened to form an azide. More typically, the epoxide at positions 3 and 4 is opened to form a 3-azido-4-hydroxy compound 278.

Typically the process comprises treating compound 277 with an azide salt in a suitable solvent. More typically, the process comprises treating
25 compound 277 with sodium azide and a mild base, such as an ammonium halide, in a polar, protic solvent, such as an alkanol or water. Still more typically, the process comprises treating compound 277 with sodium azide and ammonium chloride in water/methanol solution to produce compound
30 278.

An exemplary embodiment of this process is given as Example 60 below.

Process K, Scheme 38

35 Compound 278 is used to prepare compound 279 by the following process.

The hydroxy group at position 4 of compound 278 is displaced by the 3-azido group to form the aziridine compound 279.

Typically the process comprises treating compound 278 with a hydroxy activating group as described above, an organophosphine and a base. More typically the process comprises treating compound 278 with a sulfonic acid halide, such as those described above, to form an activated hydroxy compound, treating the activated hydroxy compound with trialkyl or triarylphosphine, such as triphenylphosphine, to form a phosphonium salt, and treating the phosphonium salt with a base, such as an amine, to form compound 279. Still more typically, the process comprises treating compound 278 with mesyl chloride, to form an activated hydroxy compound, treating the activated hydroxy compound with triphenylphosphine, to form a phosphonium salt, and treating the phosphonium salt with triethylamine and H₂O, to form compound 279.

An exemplary embodiment of this process is given as Examples 61 and 62 below.

Process L, Scheme 38

Compound 279 is used to prepare compound 280 by the following process.

The aziridine compound 279 is opened with azide to form azido amine 280.

Typically the process comprises treating compound 279 with with an azide salt in a suitable solvent. More typically, the process comprises treating compound 279 with sodium azide and a mild base, such as an ammonium halide, in a polar, aprotic solvent, such as an ether, amine, or amide. Still more typically, the process comprises treating compound 279 with sodium azide and ammonium chloride in DMF solution to produce compound 280.

An exemplary embodiment of this process is given as Example 63 below.

Process M, Scheme 38

Compound 280 is used to prepare compound 281 by the following process.

The protected hydroxy group at position 5 is displaced by the amine at position 4 to form aziridine 281. Typically the aziridine 281 is substituted with

an acid labile group, more typically an aziridine activating group.

R54 is an acid labile group, typically an acid labile amine protecting group such as those described in the above cited work of Greene. More typically, R54 is an aziridine activating group, still more typically, a group capable of activating an aziridine toward acid catalyzed ring opening. Typical R54 groups include by way of example and not limitation, a linear or branched 1-oxo-alk-1-yl group of 1 to 12 carbons wherein the alkyl portion is a 1 to 11 carbon linear or branched chain alkyl group (such as $\text{CH}_3(\text{CH}_2)_z\text{C}(\text{O})-$, z is an integer from 0 to 10, i.e. acetyl $\text{CH}_3\text{C}(\text{O})-$, etc.), substituted methyl (e.g. triphenylmethyl, $\text{Ph}_3\text{C}-$, trityl, Tr), or a carbamate such as BOC or Cbz or a sulfonate (e.g. alkyl sulphonates such as methyl sulphonate). More typical R54 groups include triphenylmethyl and 1-oxo-alk-1-yl groups having 1 to 8, still more typically, 1, 2, 3, 4, 5, or 6, more typically yet, 2 or 3 carbon atoms.

Typically the process comprises treating compound 280 with a deprotecting agent to remove group R53, an R54 producing reagent such as those described in Greene (R54-halide, such as acetylchloride, or $\text{Tr}-\text{Cl}$, or $\text{R54}-\text{O}-\text{R54}$, such as acetic anhydride), and a hydroxy activating group such as those described in process B, Scheme 36. More typically the process comprises treating compound 280 with a polar, protic solvent, optionally in the presence of an acid catalyst as described above, to form a first intermediate; treating the first intermediate with $\text{Tr}-\text{Cl}$ in a polar, aprotic solvent, such as an amine, to form a second intermediate; and treating the second intermediate with a sulfonic acid halide, such as mesyl chloride or para toluene sulfonyl chloride, in a polar aprotic solvent, such as an amine, to produce compound 281. Still more typically, the process comprises treating compound 280 with methanol and HCl , to form a first intermediate; treating the first intermediate with $\text{Tr}-\text{Cl}$ and triethylamine, to form a second intermediate; and treating the second intermediate with mesyl chloride and triethylamine, to produce compound 281.

An exemplary embodiment of this process is given as Example 64 below.

Process N, Scheme 39

Compound 281 is used to prepare compound 282 by the following process.

Aziridine 281 is opened and the resulting amine is substituted with an R55 group to form compound 282. Typically, aziridine 281 is opened by acid catalyzed ring opening and the resulting amine is acylated.

5 R55 is W3 as defined above. Typically R55 is -C(O)R5. More typically, R55 is -C(O)R1. Still more typically, R55 is -C(O)CH3.

R56 is U1 as described above. Typically R56 is W6-O-, W6-S-, or W6-N(H)-. More typically, R56 is R5-O-, R5-S-, or R5-N(H)-, still more typically, R56 is R5-O-, still more typically yet, R56 is R1-O-.

10 Typically the process comprises treating compound 281 with an acid catalyst and a compound of the formula W6-X1-H, wherein X1 is as defined above to form an amine intermediate; and treating the amine intermediate with a compound of the formula W3-X1-W3, W3-X10, wherein X10 is a
15 leaving group, to form compound 282. The acid catalyst is typically a Lewis acid catalyst common in the art, such as BF3•Et2O, TiCl3, TMSOTf, SmI2(THF)2, LiClO4, Mg(ClO4)2, Ln(OTf)3 (where Ln=Yb, Gd, Nd), Ti(Oi-Pr)4, AlCl3, AlBr3, BeCl2, CdCl2, ZnCl2, BF3, BCl3, BBr3, GaCl3, GaBr3, TiCl4, TiBr4, ZrCl4, SnCl4, SnBr4, SbCl5, SbCl3, BiCl3, FeCl3, UCl4, ScCl3, YCl3, LaCl3, CeCl3, PrCl3, NdCl3, SmCl3, EuCl3, GdCl3, TbCl3, LuCl3, DyCl3, HoCl3,
20 ErCl3, TmCl3, YbCl3, ZnI2, Al(OPrⁱ)3, Al(acac)3, ZnBr2, for SnCl4. X1 is typically -O-, -S-, or -N(H)-. X10 is typically a halide such as Cl, Br, or I. More typically, the process comprises treating compound 281 with a compound of the formula R5-OH, R5-SH, or R5-NH2, and BF3•Et2O to form an
25 intermediate; and treating the intermediate with an alkanoic acid anhydride to form compound 282. Still more typically, the process comprises treating compound 281 with a compound of the formula R5-OH and BF3•Et2O to form an intermediate; and treating the intermediate with a substituted or unsubstituted acetic anhydride to form compound 282. Exemplary
30 compounds of the formula R5-OH include those described by Table 2, groups 2-7, 9-10, 15, and 100-660 wherein Q1 is -OH. Further exemplary compounds of the formula R5-OH include those shown in Table 25 below (together with their Chemical Abstracts Service Registry Numbers) and those shown in Table 26 below (together with their Chemical Abstracts Service Registry
35 Numbers, and Aldrich Chemical Company Product Numbers). More typical exemplary compounds of the formula R5-OH are those described by Table 2, groups 2-5, 9, and 100-141 wherein Q1 is -OH.

In another embodiment of Process N, Scheme 39, R₅ is H.

Typically this process embodiment comprises treating compound 281 with an acid catalyst and a compound of the formula R₅-X₁-H, wherein X₁ is as defined above to form an amine intermediate to form compound 282. The acid catalyst and X₁ are as described above. More typically, the process comprises treating compound 281 with a compound of the formula R₅-OH, R₅-SH, or R₅-NH₂, and BF₃•Et₂O to form compound 282. Still more typically, the process comprises treating compound 281 with a compound of the formula R₅-OH and BF₃•Et₂O to form compound 282. Exemplary compounds of the formula R₅-OH are described above.

Exemplary embodiments of this process are given as Examples 65, 86, 92, and 95 below.

Process O, Scheme 39

Compound 282 is used to prepare compound 283 by the following process.

The azide of compound 282 is reduced to form amino compound 283.

Typically the process comprises treating compound 282 with a reducing agent to form compound 283. More typically the process comprises treating compound 282 with hydrogen gas and a catalyst (such as platinum on carbon or Lindlar's catalyst), or reducing reagents (such as a trialkyl or triaryl phosphine as described above). More typically still, the process comprises treating compound 282 with triphenylphosphine in water/THF to form compound 283.

Exemplary embodiments of this process are given as Examples 87, 93, and 96 below.

Process P, Scheme 39

Compound 283 is used to prepare compound 284 by the following process.

The carboxylic acid protecting group is removed.

Typically the process comprises treating compound 283 with a base. More typically, the process comprises treating compound 283 with a metal hydroxide in a suitable solvent such as an aprotic, polar solvent. More typically still, the process comprises treating compound 283 with aqueous potassium hydroxide in THF to produce compound 284.

Exemplary embodiments of this process are given as Examples 88, 94, and 97 below.

Process O. Scheme 40

5 Compound 283 is used to prepare compound 285 by the following process.

 The amine is converted to a protected guanidine.

 R57 is a guanidine protecting group common in the art, such as BOC or Me.

10 Typically the process comprises treating compound 283 with a guanidylating reagent such as those common in the art. Exemplary reagents include Bis-BOC Thio-Urea aminoiminomethanesulfonic acid (Kim; et al.; "Tet. Lett." 29(26):3183-3186 (1988) and 1-guanylpurazoles (Bernatowicz; et al.; "Tet. Lett." 34(21):3389-3392 (1993). More typically, the process comprises
15 treating compound 283 with Bis-BOC Thio-Urea acid. Still more typically, the process comprises treating compound 283 with Bis-BOC Thio-Urea acid and HgCl₂ to form compound 285.

 An exemplary embodiment of this process is given as Example 67 below.

20

Process R. Scheme 40

 Compound 285 is used to prepare compound 286 by the following process.

 The carboxylic acid and guanidine protecting groups are removed.

25 Typically the process comprises treating compound 285 with a base; followed by treating with an acid, as described above. More typically the process comprises treating compound 285 with a metal hydroxide base, described above, to form an intermediate; and treating the intermediate with
30 treating compound 285 with aqueous potassium hydroxide and THF, to form an intermediate; and treating the intermediate with TFA to form compound 286.

Process S. Scheme 40.1

35 Compound 287 is used to prepare compound 288 by the following process.

E1, J1 and J2 of compounds 287 and 288 are as described above. Typically, E1 is -CO₂R₅₁ as described above. Typically, J1 is H, F, or methyl, more typically, H. Typically, J2 is H or a linear or branched alkyl of 1 to 6 carbon atoms, more typically, H, methyl, ethyl, n-propyl, or i-propyl, still
5 more typically, H.

R₆₀ and R₆₁ are groups capable of reacting to form the R₆₃ (defined below) substituted aziridine ring of compound 288. Typically, one of R₆₀ or R₆₁ is a primary or secondary amine, or a group capable of being converted to a primary or secondary amine. Such groups for R₆₀ and R₆₁ include by way
10 of example and not limitation, -NH₂, -N(H)(R_{6b}), -N(R_{6b})₂, -N(H)(R₁), -N(R₁)(R_{6b}), and -N₃. The other of R₆₀ and R₆₁ is typically a group capable of being displaced by a primary or secondary amine to form an aziridine. Such groups include by way of example and not limitation, -OH, -OR_{6a}, Br, Cl, and I. Typically, R₆₀ and R₆₁ are in a trans configuration. More typically, R₆₀ is a
15 primary or secondary amine, or a group capable of being converted to a primary or secondary amine and R₆₁ is a group capable of being displaced by a primary or secondary amine to form an aziridine. Still more typically, R₆₀ is β-azido or β-NH₂, and R₆₁ is α-OH, α-OMesyl, or α-OTosyl.

R₆₂ is described below in Process U, Scheme 40.1.

The process comprises treating compound 287 to form compound 288. This is typically accomplished by treating compound 287 to displace R₆₁ by R₆₀. More typically, compound 287 is treated to activate R₆₁ toward displacement by R₆₀. Still more typically, compound 287 is treated to activate R₆₁ toward displacement by R₆₀, and R₆₀ is activated toward displacement of
25 R₆₁. If both R₆₀ and R₆₁ are activated, the activations can be performed simultaneously or sequentially. If the activations are performed sequentially, they can be performed in any order, typically the activation of R₆₁ precedes the activation of R₆₀.

Activation of R₆₁ toward displacement by R₆₀ is typically accomplished
30 by treating compound 287 with a hydroxy activating reagent such as mesyl or tosyl chloride. Activation of R₆₀ toward displacement of R₆₁ is typically accomplished by treating compound 287 to form a primary or secondary amine and treating the amine with a base. By way of example and not limitation, compound 287 is treated with a reducing agent capable of reducing
35 an azide to an amine and a base.

In one embodiment of this process, compound 287 is treated with an R₆₁ activating reagent, and an R₆₀ activating reagent to produce compound 288. In another embodiment, compound 287 is treated in a suitable solvent
5 with an R₆₁ activating reagent, and an R₆₀ activating reagent to produce compound 288. In another embodiment, compound 287 is treated with an R₆₁ activating reagent, an R₆₀ activating reagent, and a base to produce compound 288. In another embodiment, compound 287 is treated in a suitable solvent with an R₆₁ activating reagent, an R₆₀ activating reagent, and
10 a base to produce compound 288. In another embodiment, compound 287 wherein R₆₀ is an azide is treated with an R₆₁ activating reagent, and an azide reducing reagent to produce compound 288. In another embodiment, compound 287 wherein R₆₀ is an azide is treated in a suitable solvent with an R₆₁ activating reagent, and an azide reducing reagent to produce compound
15 288. In another embodiment, compound 287 wherein R₆₀ is an azide is treated with an R₆₁ activating reagent, an azide reducing reagent, and a base to produce compound 288. In another embodiment, compound 287 wherein R₆₀ is an azide is treated in a suitable solvent with an R₆₁ activating reagent, an azide reducing reagent, and a base to produce compound 288. In another
20 embodiment, compound 287 wherein R₆₀ is an azide and R₆₁ is a hydroxy, is treated with a hydroxy activating reagent, and an azide reducing reagent to produce compound 288. In another embodiment, compound 287 wherein R₆₀ is an azide and R₆₁ is a hydroxy, is treated in a suitable solvent with an hydroxy activating reagent, and an azide reducing reagent to produce
25 compound 288. In another embodiment, compound 287 wherein R₆₀ is an azide and R₆₁ is a hydroxy, is treated with a hydroxy activating reagent, an azide reducing reagent, and a base to produce compound 288. In another embodiment, compound 287 wherein R₆₀ is an azide and R₆₁ is a hydroxy, is treated in a suitable solvent with a hydroxy activating reagent, an azide
30 reducing reagent, and a base to produce compound 288.

An exemplary embodiments of this process are given as Process K, Scheme 38, above.

Process T, Scheme 40.1

35 Compound 288 is used to prepare compound 289 by the following process.

R₆₄ is typically H, R_{6b} or a group capable of being converted to H or R_{6b}. More typically, R₆₄ is H. R₆₅ is typically G₁ or a group capable of being converted to G₁. More typically, R₆₅ is -N₃, -CN, or -(CR₁R₁)_{m1}W₂. More typically R₆₅ is -N₃, -NH₂, -N(H)(R_{6b}), -N(R_{6b})₂, -CH₂N₃, or -CH₂CN.

Typically, compound 288 is treated to form amine 289. More typically, compound 288 is treated with a nucleophile, typically a nitrogen nucleophile such as R₆₅, a cationic salt of R₆₅, or a protonated analog of R₆₅, such as by way of example and not limitation, NH₃, an azide salt (such as NaN₃, KN₃, or the like), HCN, a cyanide salt (such as NaCN, KCN, or the like), or a salt of a cyanoalkyl (e.g. (CH₂CN)⁻) (such as NaCH₂CN, KCH₂CN, or the like). Still more typically, compound 288 is treated with an azide salt. Optionally a base, typically a mild base such as an ammonium halide and a solvent, typically a polar, aprotic solvent, such as an ether, amine, or amide are used.

In one embodiment, compound 288 is treated with a nucleophile. In another embodiment, compound 288 is treated with a nucleophile in a suitable solvent to produce compound 289. In another embodiment, compound 288 is treated with a nucleophile and a base to produce compound 289. In another embodiment, compound 288 is treated with a nucleophile and a base in a suitable solvent to produce compound 289. In another embodiment, compound 288 is treated with a nitrogen nucleophile to produce compound 289. In another embodiment, compound 288 is treated with a nitrogen nucleophile in a suitable solvent to produce compound 289. In another embodiment, compound 288 is treated with a nitrogen nucleophile and a base to produce compound 289. In another embodiment, compound 288 is treated with a nitrogen nucleophile and a base in a suitable solvent to produce compound 289. In another embodiment, compound 288 is treated with an azide salt to produce compound 289. In another embodiment, compound 288 is treated with an azide salt in a suitable solvent to produce compound 289. In another embodiment, compound 288 is treated with an azide salt and a base to produce compound 289. In another embodiment, compound 288 is treated with an azide salt and a base in a suitable solvent to produce compound 289.

An exemplary embodiment of this process is given as Process L, Scheme 38, above.

Process U. Scheme 40.1

Compound 289 is used to prepare compound 290 by the following process.

5 R₆₂ is a group capable of reacting with an amine to form the R₆₆ (defined below) substituted aziridine ring of compound 290. Typically, R₆₂ is a group capable of being displaced by a primary or secondary amine to form an aziridine. Such groups include by way of example and not limitation, -OR₅₃, -OH, -OR_{6a}, Br, Cl, and I. Typically, R₆₂ is in a trans configuration relative to
10 the nitrogen in position 4. More typically, R₆₂ is -OR₅₃.

 R₆₄ is H or R_{6b}, typically an acid labile protecting group such as R₅₄.

 R₆₆ is H, R_{6b} or R₅₄.

 The process comprises treating compound 289 to form compound 290. This is typically accomplished by treating compound 289 to displace R₆₂ by the
15 amine at position 4. More typically, compound 289 is treated to activate the amine at position 4 toward displacement of R₆₂. Still more typically, compound 289 is treated to activate the amine at position 4 toward displacement of R₆₂, and R₆₂ is activated toward displacement by the amine at position 4. If both R₆₂ and the amine at position 4 are activated, the
20 activations can be performed simultaneously or sequentially. If the activations are performed sequentially, they can be performed in any order, typically the activation of R₆₂ precedes the activation of the amine at position 4.

 Activation of R₆₂ toward displacement by the amine at position 4 is
25 typically accomplished by treating compound 289 with a hydroxy activating agent such as those described in process B, Scheme 36. Optionally, R₆₂ is deprotected prior to activation. Activation of the amine at position 4 toward R₆₂ displacement is typically accomplished by treating compound 289 to form a primary or secondary amine and treating the amine with an acid catalyst
30 such as those described in Process N, Scheme 39, above..

 Typically when R₆₂ is -OR₅₃ and R₆₆ is R₅₆, the process comprises treating compound 289 with a deprotecting agent to remove group R₅₃, an R₅₄ producing reagent such as those described in Greene (R₅₄-halide, such as acetylchloride, or Tr-Cl, or R₅₄-O-R₅₄, such as acetic anhydride), and a
35 hydroxy activating group such as those described in Process B, Scheme 36. More typically the process comprises treating compound 289 with a polar, protic solvent, optionally in the presence of an acid catalyst as described above,

to form a first intermediate; treating the first intermediate with Tr-Cl in a polar, aprotic solvent, such as an amine, to form a second intermediate; and treating the second intermediate with a sulfonic acid halide, such as mesyl chloride or para toluene sulfonyl chloride, in a polar aprotic solvent, such as an amine, to produce compound 290. Still more typically, the process comprises treating compound 289 with methanol and HCl, to form a first intermediate; treating the first intermediate with Tr-Cl and triethylamine, to form a second intermediate; and treating the second intermediate with mesyl chloride and triethylamine, to produce compound 290.

In one embodiment compound 289 is treated with an acid catalyst to produce compound 290. In another embodiment compound 289 is treated with an acid catalyst in a suitable solvent to produce compound 290. In another embodiment compound 289 is treated with a hydroxy activating reagent and an acid catalyst to produce compound 290. In another embodiment compound 289 is treated with a hydroxy activating reagent and an acid catalyst in a suitable solvent to produce compound 290. In another embodiment compound 289 is treated with a hydroxy deprotecting reagent, a hydroxy activating reagent and an acid catalyst to produce compound 290. In another embodiment compound 289 is treated with a hydroxy activating reagent and an acid catalyst in a suitable solvent to produce compound 290.

An exemplary embodiment of this process is given as Process M, Scheme 38, above.

Process V, Scheme 40.1

Compound 290 is used to prepare compound 291 by the following process.

Aziridine 290 is treated to form compound 291. Typically, aziridine 290 is opened by acid catalyzed ring opening and the resulting amine is acylated.

R₆₈ is independently H, R_{6b}, R₁ or R₅₅ as defined above. Typically R₅₅ is -C(O)R₅. Typically one R₆₈ is H or R_{6b} and the other is W₃.

R₆₇ is U₁ as described above. Typically R₆₇ is W₆-O-, W₆-S-, or W₆-N(H)-. More typically, R₆₇ is R₅-O-, R₅-S-, or R₅-N(H)-.

Typically the process comprises treating compound 290 with an acid catalyst and a compound of the formula W₆-X₁-H, wherein X₁ is as defined above to form an amine intermediate; and treating the amine intermediate with a compound of the formula W₃-X₁-W₃, or W₃-X₁₀, wherein X₁₀ is a leaving group, to form compound 291. The treatment with a compound of

the formula W_6-X_1-H and an acid catalyst may be prior to or simultaneous with the treatment with a compound of the formula $W_3-X_1-W_3$, or W_3-X_{10} . The acid catalyst is typically one of those described in Process N, **Scheme 39**, above. More typically, the process comprises treating compound **290** with a
5 compound of the formula R_5-OH , R_5-SH , or R_5-NH_2 and an acid catalyst; and treating the intermediate with an alkanolic acid anhydride to form compound **291**.

One embodiment comprises treating compound **290** with a compound of the formula W_6-X_1-H and an acid catalyst to produce compound **291**.
10 Another embodiment comprises treating compound **290** with a compound of the formula W_6-X_1-H and an acid catalyst in a suitable solvent to produce compound **291**. Another embodiment comprises treating compound **290** with a compound of the formula W_6-X_1-H , an acid catalyst and a compound of the formula $W_3-X_1-W_3$ or W_3-X_{10} to produce compound **291**. Another
15 embodiment comprises treating compound **290** with a compound of the formula W_6-X_1-H , an acid catalyst and a compound of the formula $W_3-X_1-W_3$ or W_3-X_{10} in a suitable solvent to produce compound **291**.

Exemplary embodiments of this process are given as Process N, **Scheme 39**, above.

20 **Process W, Scheme 40.1**

Compound **291** is used to prepare compound **292** by the following process.

Compound **291** is treated to form compound **292**. Typically R_{65} is
25 converted to form G_1 . U_1 is an embodiment of R_{67} and T_1 is an embodiment of $-N(R_{68})_2$ prepared in Process V, **Scheme 40.1**, above.

In one embodiment, R_{65} is deprotected, alkylated, guanidinylation, oxidized or reduced to form G_1 . Any number of such treatments can be performed in any order or simultaneously. By way of example and not
30 limitation, when R_{65} is azido, embodiments of this process include Processes O, OQ, OQR, and OP. Typical alkylating agents are those common in the art including, by way of example and not limitation, an alkyl halide such as methyl iodide, methyl bromide, ethyl iodide, ethyl bromide, n-propyl iodide, n-propyl bromide, i-propyl iodide, i-propyl bromide; and an olefin oxide such
35 as ethylene oxide or propylene oxide. A base catalyst as described herein maybe optionally employed in the alkylation step.

One embodiment comprises treating compound 291 wherein R₆₅ is azido with a reducing agent to produce compound 292. Another embodiment comprises treating compound 291 wherein R₆₅ is azido with a reducing agent to produce compound 292 in a suitable solvent. Another embodiment comprises treating compound 291 wherein R₆₅ is amino with an alkylating agent to produce compound 292. Another embodiment comprises treating compound 291 wherein R₆₅ is amino with an alkylating agent to produce compound 292 in a suitable solvent. Another embodiment comprises treating compound 291 wherein R₆₅ is azido with a reducing agent and an alkylating agent to produce compound 292. Another embodiment comprises treating compound 291 wherein R₆₅ is azido with a reducing agent and an alkylating agent to produce compound 292 in a suitable solvent. Another embodiment comprises treating compound 291 wherein R₆₅ is amino with an alkylating agent and a base catalyst to produce compound 292. Another embodiment comprises treating compound 291 wherein R₆₅ is amino with an alkylating agent and a base catalyst to produce compound 292 in a suitable solvent. Another embodiment comprises treating compound 291 wherein R₆₅ is azido with a reducing agent, an alkylating agent and a base catalyst to produce compound 292. Another embodiment comprises treating compound 291 wherein R₆₅ is azido with a reducing agent, an alkylating agent and a base catalyst to produce compound 292 in a suitable solvent.

Exemplary embodiments of this process are given as Process O, Scheme 39, above.

Exemplary embodiments of this process are given as Examples 68 and 69 below.

Table 25 - Exemplary Compounds of Formula R₅-OH (CAS No.)C4 Fluoro Alcohols

- (R*,R*)-(±)-3-fluoro-2-Butanol (139755-61-6)
- 5 1-fluoro-2-Butanol (124536-12-5)
- (R)-3-fluoro-1-Butanol (120406-57-7)
- 3-fluoro-1-Butanol (19808-95-8)
- 4-fluoro-2-Butanol (18804-31-4)
- (R*,S*)-3-fluoro-2-Butanol (6228-94-0)
- 10 (R*,R*)-3-fluoro-2-Butanol (6133-82-0)
- 2-fluoro-1-Butanol (4459-24-9)
- 2-fluoro-2-methyl-1-Propanol (3109-99-7)
- 3-fluoro-2-Butanol (1813-13-4)
- 4-fluoro-1-Butanol (372-93-0)
- 15 1-fluoro-2-methyl-2-Propanol (353-80-0)

C5 Fluoro Alcohols

- 2-fluoro-1-Pentanol (123650-81-7)
- (R)-2-fluoro-3-methyl-1-Butanol (113943-11-6)
- 20 (S)-2-fluoro-3-methyl-1-Butanol (113942-98-6)
- 4-fluoro-3-methyl-1-Butanol (104715-25-5)
- 1-fluoro-3-Pentanol (30390-84-2)
- 4-fluoro-2-Pentanol (19808-94-7)
- 5-fluoro-2-Pentanol (18804-35-8)
- 25 3-fluoro-2-methyl-2-Butanol (7284-96-0)
- 2-fluoro-2-methyl-1-Butanol (4456-02-4)
- 3-fluoro-3-methyl-2-Butanol (1998-77-2)
- 5-fluoro-1-Pentanol (592-80-3)

30 C6 Fluoro Alcohols

- (R-(R*,S*))-(±)-2-fluoro-3-methyl-1-Pentanol (168749-88-0)
- 1-fluoro-2,3-dimethyl-2-Butanol (161082-90-2)
- 2-fluoro-2,3-dimethyl-1-Butanol (161082-89-9)
- (R)-2-fluoro-4-methyl-1-Pentanol (157988-30-2)
- 35 (S-(R*,R*))-(±)-2-fluoro-3-methyl-1-Pentanol (151717-18-9)
- (R*,S*)-2-fluoro-3-methyl-1-Pentanol (151657-14-6)
- (S)-2-fluoro-3,3-dimethyl-1-Butanol (141022-94-8)
- (M)-2-fluoro-2-methyl-1-Pentanol (137505-57-8)
- (S)-2-fluoro-1-Hexanol (127608-47-3)
- 40 3-fluoro-3-methyl-1-Pentanol (112754-22-0)
- 3-fluoro-2-methyl-2-Pentanol (69429-54-5)
- 2-fluoro-2-methyl-3-Pentanol (69429-53-4)
- 1-fluoro-3-Hexanol (30390-85-3)
- 5-fluoro-2-methyl-2-Pentanol (21871-78-3)
- 45 5-fluoro-3-Hexanol (19808-92-5)
- 4-fluoro-3-methyl-2-Pentanol (19808-90-3)

- 4-fluoro-4-methyl-2-Pentanol (19031-69-7)
1-fluoro-3,3-dimethyl-2-Butanol (4604-66-4)
2-fluoro-2-methyl-1-Pentanol (4456-03-5)
2-fluoro-4-methyl-1-Pentanol (4455-95-2)
5 2-fluoro-1-Hexanol (1786-48-7)
3-fluoro-2,3-dimethyl-2-Butanol (661-63-2)
6-fluoro-1-Hexanol (373-32-0)

C7 Fluoro Alcohols

- 10 5-fluoro-5-methyl-1-Hexanol (168268-63-1)
(R)-1-fluoro-2-methyl-2-Hexanol (153683-63-7)
(S)-3-fluoro-1-Heptanol (141716-56-5)
(S)-2-fluoro-2-methyl-1-Hexanol (132354-09-7)
(R)-3-fluoro-1-Heptanol (120406-54-4)
15 (S)-2-fluoro-1-Heptanol (110500-31-7)
1-fluoro-3-Heptanol (30390-86-4)
7-fluoro-2-Heptanol (18804-38-1)
2-ethyl-2-(fluoromethyl)-1-Butanol (14800-35-2)
2-(fluoromethyl)-2-methyl-1-Pentanol (13674-80-1)
20 2-fluoro-5-methyl-1-Hexanol (4455-97-4)
2-fluoro-1-Heptanol (1786-49-8)
7-fluoro-1-Heptanol (408-16-2)

C8 Fluoro Alcohols

- 25 (M)-2-fluoro-2-methyl-1-Heptanol (137505-55-6)
6-fluoro-6-methyl-1-Heptanol (135124-57-1)
1-fluoro-2-Octanol (127296-11-1)
(R)-2-fluoro-1-Octanol (118205-91-7)
(±)-2-fluoro-2-methyl-1-Heptanol (117169-40-1)
30 (S)-2-fluoro-1-Octanol (110500-32-8)
(S)-1-fluoro-2-Octanol (110270-44-5)
(R)-1-fluoro-2-Octanol (110270-42-3)
(±)-1-fluoro-2-Octanol (110229-70-4)
2-fluoro-4-methyl-3-Heptanol (87777-41-1)
35 2-fluoro-6-methyl-1-Heptanol (4455-99-6)
2-fluoro-1-Octanol (4455-93-0)
8-fluoro-1-Octanol (408-27-5)

C9 Fluoro Alcohols

- 40 6-fluoro-2,6-dimethyl-2-Heptanol (160981-64-6)
(S)-3-fluoro-1-Nonanol (160706-24-1)
(R-(R*,R*))-3-fluoro-2-Nonanol (137909-46-7)
(R-(R*,S*))-3-fluoro-2-Nonanol (137909-45-6)
3-fluoro-2-Nonanol (137639-20-4)
45 (S-(R*,R*))-3-fluoro-2-Nonanol (137639-19-1)
(S-(R*,S*))-3-fluoro-2-Nonanol (137639-18-0)
(±)-3-fluoro-1-Nonanol (134056-76-1)

- 2-fluoro-1-Nonanol (123650-79-3)
2-fluoro-2-methyl-1-Octanol (120400-89-7)
(R)-2-fluoro-1-Nonanol (118243-18-8)
(S)-1-fluoro-2-Nonanol (111423-41-7)
5 (S)-2-fluoro-1-Nonanol (110500-33-9)
1-fluoro-3-Nonanol (30390-87-5)
2-fluoro-2,6-dimethyl-3-Heptanol (684-74-2)
9-fluoro-1-Nonanol (463-24-1)
- 10 C10 Fluoro Alcohols
4-fluoro-1-Decanol (167686-45-5)
(P)-10-fluoro-3-Decanol (145438-91-1)
(R-(R*,R*))-3-fluoro-5-methyl-1-Nonanol (144088-79-9)
(P)-10-fluoro-2-Decanol (139750-57-5)
15 1-fluoro-2-Decanol (130876-22-1)
(S)-2-fluoro-1-Decanol (127608-48-4)
(R)-1-fluoro-2-Decanol (119105-16-7)
(S)-1-fluoro-2-Decanol (119105-15-6)
2-fluoro-1-Decanol (110500-35-1)
20 1-fluoro-5-Decanol (106533-31-7)
4-fluoro-2,2,5,5-tetramethyl-3-Hexanol (24212-87-1)
10-fluoro-1-Decanol (334-64-5)
- C11 Fluoro Alcohols
25 10-fluoro-2-methyl-1-Decanol (139750-53-1)
2-fluoro-1-Undecanol (110500-34-0)
8-fluoro-5,8-dimethyl-5-Nonanol (110318-90-6)
11-fluoro-2-Undecanol (101803-63-8)
11-fluoro-1-Undecanol (463-36-5)
30
- C12 Fluoro Alcohols
11-fluoro-2-methyl-1-Undecanol (139750-52-0)
1-fluoro-2-Dodecanol (132547-33-2)
(R*,S*)-7-fluoro-6-Dodecanol (130888-52-7)
35 (R*,R*)-7-fluoro-6-Dodecanol (130876-18-5)
(S)-2-fluoro-1-Dodecanol (127608-49-5)
12-fluoro-2-pentyl--Heptanol (120400-91-1)
(R*,S*)-(±)-7-fluoro-6-Dodecanol (119174-39-9)
(R*,R*)-(±)-7-fluoro-6-Dodecanol (119174-38-8)
40 2-fluoro-1-Dodecanol (110500-36-2)
11-fluoro-2-methyl-2-Undecanol (101803-67-2)
1-fluoro-1-Dodecanol (100278-87-3)
12-fluoro-1-Dodecanol (353-31-1)
- 45 C4 Nitro Alcohols
(R)-4-nitro-2-Butanol (129520-34-9)
(S)-4-nitro-2-Butanol (120293-74-5)

- 4-nitro-1-Butanol radical ion(1-) (83051-13-2)
(R*,S*)-3-nitro-2-Butanol (82978-02-7)
(R*,R*)-3-nitro-2-Butanol (82978-01-6)
4-nitro-1-Butanol (75694-90-5)
5 (±)-4-nitro-2-Butanol (72959-86-5)
4-nitro-2-Butanol (55265-82-2),
1-aci-nitro-2-Butanol (22916-75-2)
3-aci-nitro-2-Butanol (22916-74-1)
2-methyl-3-nitro-1-Propanol (21527-52-6)
10 3-nitro-2-Butanol (6270-16-2)
2-methyl-1-nitro-2-Propanol (5447-98-3)
2-aci-nitro-1-Butanol (4167-97-9)
1-nitro-2-Butanol (3156-74-9)
2-nitro-1-Butanol (609-31-4)
15 2-methyl-2-nitro-1-Propanol (76-39-1)

C5 Nitro Alcohols

- (R)-3-methyl-3-nitro-2-Butanol (154278-27-0)
3-methyl-1-nitro-1-Butanol (153977-20-9)
20 (±)-1-nitro-3-Pentanol (144179-64-6)
(S)-1-nitro-3-Pentanol (144139-35-5)
(R)-1-nitro-3-Pentanol (144139-34-4)
(R)-3-methyl-1-nitro-2-Butanol (141434-98-2)
(±)-3-methyl-1-nitro-2-Butanol (141377-55-1)
25 (R*,R*)-3-nitro-2-Pentanol (138751-72-1)
(R*,S*)-3-nitro-2-Pentanol (138751-71-0)
(R*,R*)-2-nitro-3-Pentanol (138668-26-5)
(R*,S*)-2-nitro-3-Pentanol (138668-19-6)
3-nitro-1-Pentanol (135462-98-5)
30 (R)-5-nitro-2-Pentanol (129520-35-0)
(S)-5-nitro-2-Pentanol (120293-75-6)
4-nitro-1-Pentanol (116435-64-4)
(±)-3-methyl-3-nitro-2-Butanol (114613-30-8)
(S)-3-methyl-3-nitro-2-Butanol (109849-50-5)
35 3-methyl-4-nitro-2-Butanol (96597-30-7)
(±)-5-nitro-2-Pentanol (78174-81-9)
2-methyl-2-nitro-1-Butanol (77392-55-3)
3-methyl-2-nitro-1-Butanol (77392-54-2)
3-methyl-4-nitro-1-Butanol (75694-89-2)
40 2-methyl-4-nitro-2-Butanol (72183-50-7)
3-methyl-3-nitro-1-Butanol (65102-50-3)
5-nitro-2-Pentanol (54045-33-9)
2-methyl-3-aci-nitro-2-Butanol (22916-79-6)
2-methyl-1-aci-nitro-2-Butanol (22916-78-5)
45 2-methyl-3-nitro-2-Butanol (22916-77-4)
2-methyl-1-nitro-2-Butanol (22916-76-3)
5-nitro-1-Pentanol (21823-27-8)

- 2-methyl-3-nitro-1-Butanol (21527-53-7)
2-nitro-3-Pentanol (20575-40-0)
3-methyl-3-nitro-2-Butanol (20575-38-6)
3-nitro-2-Pentanol (5447-99-4)
5 2-nitro-1-Pentanol (2899-90-3)
3-methyl-1-nitro-2-Butanol (2224-38-6)
1-nitro-2-Pentanol (2224-37-5)
- 10 C6 Nitro Alcohols
(-)-4-methyl-1-nitro-2-Pentanol (158072-33-4)
3-(nitromethyl)-3-Pentanol (156544-56-8)
(R*,R*)-3-methyl-2-nitro-3-Pentanol (148319-17-9)
(R*,S*)-3-methyl-2-nitro-3-Pentanol (148319-16-8)
15 6-nitro-2-Hexanol (146353-95-9)
(±)-6-nitro-3-Hexanol (144179-63-5)
(S)-6-nitro-3-Hexanol (144139-33-3)
(R)-6-nitro-3-Hexanol (144139-32-2)
3-nitro-2-Hexanol (127143-52-6)
20 5-nitro-2-Hexanol (110364-37-9)
4-methyl-1-nitro-2-Pentanol (102014-44-8)
(R*,S*)-2-methyl-4-nitro-3-Pentanol (82945-29-7)
(R*,R*)-2-methyl-4-nitro-3-Pentanol (82945-20-8)
2-methyl-5-nitro-2-Pentanol (79928-61-3)
25 2,3-dimethyl-1-nitro-2-Butanol (68454-59-1)
2-methyl-3-nitro-2-Pentanol (59906-62-6)
3,3-dimethyl-1-nitro-2-Butanol (58054-88-9)
2,3-dimethyl-3-nitro-2-Butanol (51483-61-5)
2-methyl-1-nitro-2-Pentanol (49746-26-1)
30 3,3-dimethyl-2-nitro-1-Butanol (37477-66-0)
6-nitro-1-Hexanol (31968-54-4)
2-methyl-3-nitro-1-Pentanol (21527-55-9)
2,3-dimethyl-3-nitro-1-Butanol (21527-54-8)
2-methyl-4-nitro-3-Pentanol (20570-70-1)
35 2-methyl-2-nitro-3-Pentanol (20570-67-6)
2-nitro-3-Hexanol (5448-00-0)
4-nitro-3-Hexanol (5342-71-2)
4-methyl-4-nitro-1-Pentanol (5215-92-9)
1-nitro-2-Hexanol (2224-40-0)
40 C7 Nitro Alcohols
1-nitro-4-Heptanol (167696-66-4)
(R)-1-nitro-2-Heptanol (146608-19-7)
7-nitro-1-Heptanol (133088-94-5)
45 (R*,S*)-3-nitro-2-Heptanol (127143-73-1)
(R*,R*)-3-nitro-2-Heptanol (127143-72-0)
(R*,S*)-2-nitro-3-Heptanol (127143-71-9)

- (R*,R*)-2-nitro-3-Heptanol (127143-70-8)
 (R*,S*)-2-methyl-5-nitro-3-Hexanol (103077-95-8)
 (R*,R*)-2-methyl-5-nitro-3-Hexanol (103077-87-8)
 3-ethyl-4-nitro-1-Pentanol (92454-38-1)
 5 3-ethyl-2-nitro-3-Pentanol (77922-54-4)
 2-nitro-3-Heptanol (61097-77-6)
 2-methyl-1-nitro-3-Hexanol (35469-17-1)
 2-methyl-4-nitro-3-Hexanol (20570-71-2)
 2-methyl-2-nitro-3-Hexanol (20570-69-8)
 10 5-methyl-5-nitro-2-Hexanol (7251-87-8)
 1-nitro-2-Heptanol (6302-74-5)
 3-nitro-4-Heptanol (5462-04-4)
 4-nitro-3-Heptanol (5342-70-1)
- 15 C8 Nitro Alcohols
 (±)-1-nitro-3-Octanol (141956-93-6)
 1-nitro-4-Octanol (167642-45-7)
 (S)-1-nitro-4-Octanol (167642-18-4)
 6-methyl-6-nitro-2-Heptanol (142991-77-3)
 20 (R*,S*)-2-nitro-3-Octanol (135764-74-8)
 (R*,R*)-2-nitro-3-Octanol (135764-73-7)
 5-nitro-4-Octanol (132272-46-9)
 (R*,R*)-3-nitro-4-Octanol (130711-79-4)
 (R*,S*)-3-nitro-4-Octanol (130711-78-3)
 25 4-ethyl-2-nitro-3-Hexanol (126939-74-0)
 2-nitro-3-Octanol (126939-73-9)
 1-nitro-3-Octanol (126495-48-5)
 (R*,R*)-(±)-3-nitro-4-Octanol (118869-22-0)
 (R*,S*)-(±)-3-nitro-4-Octanol (118869-21-9)
 30 3-nitro-2-Octanol (127143-53-7)
 (R*,S*)-2-methyl-5-nitro-3-Heptanol (103078-03-1)
 (R*,R*)-2-methyl-5-nitro-3-Heptanol (103077-90-3)
 8-nitro-1-Octanol (101972-90-1)
 (±)-2-nitro-1-Octanol (96039-95-1)
 35 3,4-dimethyl-1-nitro-2-Hexanol (64592-02-5)
 3-(nitromethyl)-4-Heptanol (35469-20-6)
 2,5-dimethyl-1-nitro-3-Hexanol (35469-19-3)
 2-methyl-1-nitro-3-Heptanol (35469-18-2)
 2,4,4-trimethyl-1-nitro-2-Pentanol (35223-67-7)
 40 2,5-dimethyl-4-nitro-3-Hexanol (22482-65-1)
 2-nitro-1-Octanol (2882-67-9)
 1-nitro-2-Octanol (2224-39-7)
- C9 Nitro Alcohols
 45 4-nitro-3-Nonanol (160487-89-8)
 (R*,R*)-3-ethyl-2-nitro-3-Heptanol (148319-18-0)
 2,6-dimethyl-6-nitro-2-Heptanol (117030-50-9)

- (R*,S*)-2-nitro-4-Nonanol (103077-93-6)
(R*,R*)-2-nitro-4-Nonanol (103077-85-6)
2-nitro-3-Nonanol (99706-65-7)
9-nitro-1-Nonanol (81541-84-6)
- 5 2-methyl-1-nitro-3-Octanol (53711-06-1)
4-nitro-5-Nonanol (34566-13-7)
2-methyl-3-(nitromethyl)-3-Heptanol (5582-88-7)
1-nitro-2-Nonanol (4013-87-0)
- 10 C10 Nitro Alcohols
2-nitro-4-Decanol (141956-94-7)
(R*,S*)-3-nitro-4-Decanol (135764-76-0)
(R*,R*)-3-nitro-4-Decanol (135764-75-9)
5,5-dimethyl-4-(2-nitroethyl)-1-Hexanol (133088-96-7)
- 15 (R*,R*)-(±)-3-nitro-4-Decanol (118869-20-8)
(R*,S*)-(±)-3-nitro-4-Decanol (118869-19-5)
5-nitro-2-Decanol (112882-29-8)
3-nitro-4-Decanol (93297-82-6)
4,6,6-trimethyl-1-nitro-2-Heptanol (85996-72-1)
- 20 2-methyl-2-nitro-3-Nonanol (80379-17-5)
1-nitro-2-Decanol (65299-35-6)
2,2,4,4-tetramethyl-3-(nitromethyl)-3-Pentanol (58293-26-8)
- C11 Nitro Alcohols
- 25 11-nitro-5-Undecanol (167696-69-7)
(R*,R*)-2-nitro-3-Undecanol (144434-56-0)
(R*,S*)-2-nitro-3-Undecanol (144434-55-9)
2-nitro-3-Undecanol (143464-92-0)
2,2-dimethyl-4-nitro-3-Nonanol (126939-76-2)
- 30 4,8-dimethyl-2-nitro-1-Nonanol (118304-30-6)
11-nitro-1-Undecanol (81541-83-5)
- C12 Nitro Alcohols
- 35 2-methyl-2-nitro-3-Undecanol (126939-75-1)
2-nitro-1-Dodecanol (62322-32-1)
1-nitro-2-Dodecanol (62322-31-0)
2-nitro-3-Dodecanol (82981-40-6)
12-nitro-1-Dodecanol (81541-78-8)

Table 26 - Exemplary Compounds of Formula R₅-OH (CAS No./Aldrich No.)

3-BROMO-1-PROPANOL	627189	167169
1,3-DICHLORO-2-PROPANOL	96231	184489
3-CHLORO-2,2-DIMETHYL-1-PROPANOL	13401564	189316
2,2-BIS(CHLOROMETHYL)-1-PROPANOL	5355544	207691
1,3-DIFLUORO-2-PROPANOL	453134	176923
2-(METHYLTHIO)ETHANOL	5271385	226424
2-(DIBUTYLAMINO)ETHANOL	102818	168491
2-(DIISOPROPYLAMINO)ETHANOL	96800	168726
3-METHYL-3-BUTEN-1-OL	763326	129402
2-METHYL-3-BUTEN-2-OL	115184	136816
3-METHYL-2-BUTEN-1-OL	556821	162353
4-HEXEN-1-OL	928927	237604
5-HEXEN-1-OL	821410	230324
CIS-2-HEXEN-1-OL	928949	224707
TRANS-3-HEXEN-1-OL	928972	224715
TRANS-2-HEXEN-1-OL	928950	132667
(+/-)-6-METHYL-5-HEPTEN-2-OL	4630062	195871
DIHYDROMYRCENOL	18479588	196428
TRANS,TRANS-2,4-HEXADIEN-1-OL	17102646	183059
2,4-DIMETHYL-2,6-HEPTADIEN-1-OL	80192569	238767
GERANIOL	106241	163333
3-BUTYN-1-OL	927742	130850
3-PENTYN-1-OL	10229104	208698
ISETHIONIC ACID, SODIUM SALT	1562001	220078
(4-(2-HYDROXYETHYL)-1-PIPERAZINE-PROPANESULFONIC ACID)	16052065	163740
HEPES, SODIUM SALT	75277393	233889
1-METHYLCYCLOPROPANEMETHANOL	2746147	236594
2-METHYLCYCLOPROPANEMETHANOL	6077721	233811
(+/-)-CHRYSANTHEMYL ALCOHOL	18383590	194654
CYCLOBUTANEMETHANOL	4415821	187917
3-CYCLOPENTYL-1-PROPANOL	767055	187275
1-ETHYNYLCYCLOPENTANOL	17356193	130869
3-METHYLCYCLOHEXANOL	591231	139734
3,3,5,5-TETRAMETHYLCYCLOHEXANOL	2650400	190624
4-CYCLOHEXYL-1-BUTANOL	4441570	197408
DIHYDROCARVEOL	619012	218421
(1S,2R,5S)-(+)-MENTHOL	15356704	224464
(1S,2S,5R)-(+)-NEOMENTHOL	2216526	235180
(1S,2R,5R)-(+)-ISOMENTHOL	23283978	242195
(+/-)-3-CYCLOHEXENE-1-METHANOL	72581329	162167
(+)-P-MENTH-1-EN-9-OL	13835308	183741
(S)-(-)-PERILLYL ALCOHOL	536594	218391
TERPINEN-4-OL	562743	218383

ALPHA-TERPINEOL	98555	218375
(+/-)-TRANS-P-MENTH-6-ENE-2,8-DIOL	32226543	247774
CYCLOHEPTANEMETHANOL	4448753	138657
TETRAHYDROFURFURYL ALCOHOL	97994	185396
(S)-(+)-2-PYRROLIDINEMETHANOL	23356969	186511
1-METHYL-2-PYRROLIDINEETHANOL	67004642	139513
1-ETHYL-4-HYDROXYPIPERIDINE	3518830	224634
3-HYDROXYPIPERIDINE HYDROCHLORIDE	64051792	174416
(+/-)-2-PIPERIDINEMETHANOL	3433372	155225
3-PIPERIDINEMETHANOL	4606659	155233
1-METHYL-2-PIPERIDINEMETHANOL	20845345	155241
1-METHYL-3-PIPERIDINEMETHANOL	7583531	146145
2-PIPERIDINEETHANOL	1484840	131520
4-HYDROXYPIPERIDINE	5382161	128775
4-METHYL-1-PIPERAZINEPROPANOL	5317339	238716
EXO-NORBORNEOL	497370	179590
ENDO-NORBORNEOL	497369	186457
5-NORBORNENE-2-METHANOL	95125	248533
(+/-)-3-METHYL-2-NORBORNANEMETHANOL	6968758	130575
((1S)-ENDO)-(-)-BORNEOL	464459	139114
(1R)-ENDO-(+)-FENCHYL ALCOHOL	2217029	196444
9-ETHYLBICYCLO(3.3.1)NONAN-9-OL	21951333	193895
(+/-)-ISOPINOCAMPHEOL	51152115	183229
(S)-CIS-VERBENOL	18881044	247065
(1R,2R,3R,5S)-(-)-ISOPINOCAMPHEOL	25465650	221902
(1R)-(-)-MYRTENOL	515004	188417
1-ADAMANTANOL	768956	130346
3,5-DIMETHYL-1-ADAMANTANOL	707379	231290
2-ADAMANTANOL	700572	153826
1-ADAMANTANEMETHANOL	770718	184209
1-ADAMANTANEETHANOL	6240115	188115
3-FURANMETHANOL	4412913	196398
FURFURYL ALCOHOL	98000	185930
2-(3-THIENYL)ETHANOL	13781674	228796
4-METHYL-5-IMIDAZOLEMETHANOL		
HYDROCHLORIDE	38585625	227420
METRONIDAZOLE	443481	226742
4-(HYDROXYMETHYL)IMIDAZOLE		
HYDROCHLORIDE	32673419	219908
4-METHYL-5-THIAZOLEETHANOL	137008	190675
2-(2-HYDROXYETHYL)PYRIDINE	103742	128643
2-HYDROXY-6-METHYLPYRIDINE	3279763	128740
4-PYRIDYLCARBINOL	586958	151629
3-PYRIDYLCARBINOL N-OXIDE	6968725	184446
1-BENZYL-4-HYDROXYPIPERIDINE	4727724	152986
1-(4-CHLOROPHENYL)-1-		
CYCLOPENTANEMETHANOL	80866791	188697

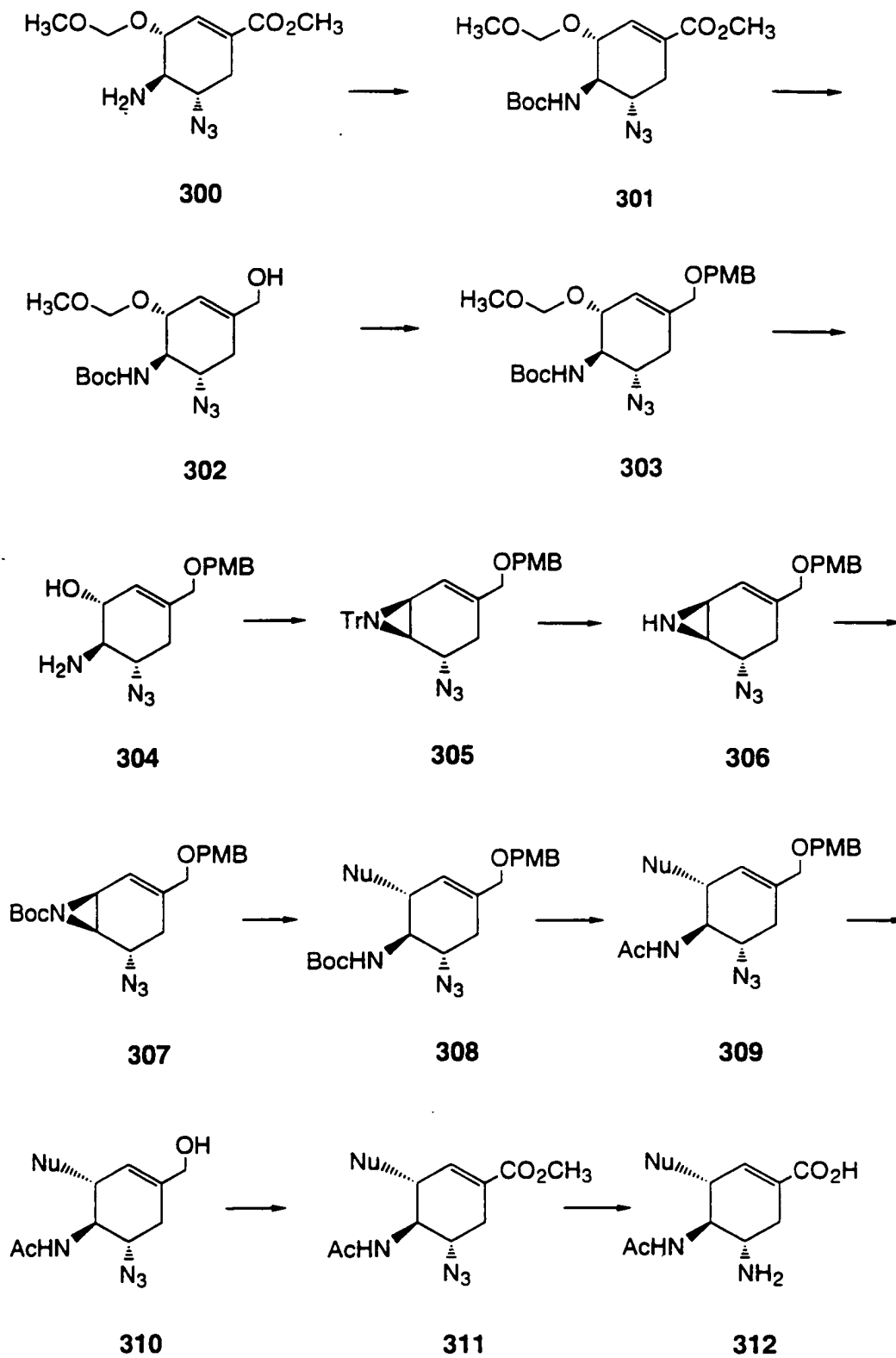
(4S,5S)-(-)-2-METHYL-5-PHENYL-2-OXAZOLINE-4-METHANOL	53732415	187666
6-(4-CHLOROPHENYL)-4,5-DIHYDRO-2-(2-HYDROXYBUTYL)-3(2H)-PYRIDAZINONE	38958826	243728
N-(2-HYDROXYETHYL)PHTHALIMIDE	3891074	138339
2-NAPHTHALENEETHANOL	1485070	188107
1-NAPHTHALENEETHANOL	773999	183458
2-ISOPROPYLPHENOL	88697	129526
4-CHLORO-ALPHA,ALPHA-DIMETHYLPHENETHYL ALCOHOL	5468973	130559
4-FLUORO-ALPHA-METHYLBENZYL ALCOHOL	403418	132705
3-PHENYL-1-PROPANOL	122974	140856
3-(4-METHOXYPHENYL)-1-PROPANOL	5406188	142328
4-FLUOROPHENETHYL ALCOHOL	7589277	154172
4-METHOXYPHENETHYL ALCOHOL	702238	154180
TRANS-2-METHYL-3-PHENYL-2-PROPEN-1-OL	1504558	155888
2-ANILINOETHANOL	122985	156876
3-FLUOROBENZYL ALCOHOL	456473	162507
2-FLUOROBENZYL ALCOHOL	446515	162515
2-METHYL-1-PHENYL-2-PROPANOL	100867	170275
ALPHA-(CHLOROMETHYL)-2,4-DICHLOROBENZYL ALCOHOL	13692143	178403
2-PHENYL-1-PROPANOL	1123859	179817
4-CHLOROPHENETHYL ALCOHOL	1875883	183423
4-BROMOPHENETHYL ALCOHOL	4654391	183431
4-NITROPHENETHYL ALCOHOL	100276	183466
2-NITROPHENETHYL ALCOHOL	15121843	183474
BETA-ETHYLPHENETHYL ALCOHOL	2035941	183482
4-PHENYL-1-BUTANOL	3360416	184756
2-METHOXYPHENETHYL ALCOHOL	7417187	187925
3-METHOXYPHENETHYL ALCOHOL	5020417	187933
3-PHENYL-1-BUTANOL	2722363	187976
2-METHYLPHENETHYL ALCOHOL	19819988	188123
3-METHYLPHENETHYL ALCOHOL	1875894	188131
4-METHYLPHENETHYL ALCOHOL	699025	188158
5-PHENYL-1-PENTANOL	10521912	188220
4-(4-METHOXYPHENYL)-1-BUTANOL	22135508	188239
4-(4-NITROPHENYL)-1-BUTANOL	79524202	188751
3,3-DIPHENYL-1-PROPANOL	20017678	188972
1-PHENYL-2-PROPANOL	14898874	189235
(+/-)-ALPHA-ETHYLPHENETHYL ALCOHOL	701702	190136
1,1-DIPHENYL-2-PROPANOL	29338496	190756
3-CHLOROPHENETHYL ALCOHOL	5182445	193518
2-CHLOROPHENETHYL ALCOHOL	19819955	193844
(+/-)-1-PHENYL-2-PENTANOL	705737	195286
2,2-DIPHENYLETHANOL	1883325	196568
4-ETHOXY-3-METHOXYPHENETHYL ALCOHOL	77891293	197599

3,4-DIMETHOXYPHENETHYL ALCOHOL	7417212	197653
3-(3,4-DIMETHOXYPHENYL)-1-PROPANOL	3929473	197688
2-(4-BROMOPHENOXY)ETHANOL	34743889	198765
2-FLUOROPHENETHYL ALCOHOL	50919067	228788
3-(TRIFLUOROMETHYL)PHENETHYL ALCOHOL	455016	230359
2-(PHENYLTHIO)ETHANOL	699127	232777
1-(2-METHOXYPHENYL)-2-PROPANOL	15541261	233773

Table 27 - Exemplary Method Embodiments of Processes A-R

A; B; C; D; I; J; K; L; M; N; O; P; Q; R; E; F; G; H; AB; BC; CD; DI; IJ; JK; KL; LM;
 5 MN; NO; OP; OQ; QR; EF; FG; GH; HI; ABC; BCD; CDI; DIJ; IJK; JKL; KLM;
 LMN; MNO; NOP; NOQ; OQR; EFG; FGH; GHI; HIJ; ABDC; BCDI; CDIJ; DIJK;
 IJKL; JKLM; KLMN; LMNO; MNOP; MNOQ; NOQR; EFHG; FGHI; GHIJ; HIJK;
 ABCDI; BCDIJ; CDIJK; DIJKL; IJKLM; JKLMN; KLMNO; LMNOP; LMNOQ;
 MNOQR; EFGHI; FGHIJ; GHIIK; HIJKL; ABCDIJ; BCDIJK; CDIJKL; DIJKLM;
 10 IJKLMN; JKLMNO; KLMNOP; KLMNOQ; LMNOQR; EFGHIJ; FGHIIK;
 GHIIKL; HIJKLM; ABCDIJK; BCDIJKL; CDIJKLM; DIJKLMN; IJKLMNO;
 JKLMNOP; JKLMNOQ; KLMNOQR; EFGHIIK; FGHIIKL; GHIIKLM;
 HIJKLMN; ABCDIJKL; BCDIJKLM; CDIJKLMN; DIJKLMNO; IJKLMNOP;
 IJKLMNOQ; JKLMNOQR; EFGHIIKL; FGHIIKLM; GHIIKLMN; HIJKLMNO;
 15 ABCDIJKLM; BCDIJKLMN; CDIJKLMNO; DIJKLMNOP; DIJKLMNOQ;
 IJKLMNOQR; EFGHIIKLM; FGHIIKLMN; GHIIKLMNO; HIJKLMNOP;
 HIJKLMNOQ; ABCDIJKLMN; BCDIJKLMNO; CDIJKLMNOP; CDIJKLMNOQ;
 DIJKLMNOQR; EFGHIIKLMN; FGHIIKLMNO; GHIIKLMNOP;
 GHIIKLMNOQ; HIJKLMNOQR; ABCDIJKLMNO; BCDIJKLMNOP;
 20 BCDIJKLMNOQ; CDIJKLMNOQR; EFGHIIKLMNO; FGHIIKLMNOP;
 FGHIIKLMNOQ; GHIIKLMNOQR; ABCDIJKLMNOP; ABCDIJKLMNOQ;
 BCDIJKLMNOQR; EFGHIIKLMNOP; EFGHIIKLMNOQ; FGHIIKLMNOQR;
 ABCDIJKLMNOQR; EFGHIIKLMNOQR; S; T; U; V; W; ST; TU; UV; VW;
 25 STU; TUV; UVW; STUV; TUVW; STUVW.

Scheme 41



Scheme 41

The amine 300 (an intermediate in Example 52, optionally purified prior to use) is treated with Boc anhydride to give the mono Boc protected amine 301. Such a transformation is found in Greene, T.W. "Protective Groups in Organic Synthesis" 2nd Ed. (John Wiley & Sons, New York, 1991) pages 327-328.

Methyl ester 301 is reduced to the corresponding primary allylic alcohol 302 with DIBAL at low temperature. Such a conversion is described by Garner, P. and Park, J. M., "J. Org. Chem.", 52:2361 (1987).

The primary alcohol 302 is protected as its *p*-methoxy benzyl ether derivative 303 by treatment with 4-methoxybenzyl chloride under basic conditions. Such a conversion is described in Horita, K. et. al., "Tetrahedron", 42:3021 (1986).

The MOM and Boc protecting groups of 303 are removed by treatment with TFA/CH₂Cl₂ to give the amino alcohol 304. Such transformations are found in Greene, T.W. "Protective Groups in Organic Synthesis", 2nd. Ed. (John Wiley & Sons, New York, 1991).

Conversion of 304 into the corresponding trityl protected aziridine 305 is accomplished in a one pot reaction two step sequence: 1) TrCl/TEA, 2) MsCl/TEA. Such a transformation has been previously described.

Aziridine 305 is then converted the corresponding Boc protected derivative 307 by first removal of the trityl group with HCl/acetone to give 306. Such a transformation is described in Hanson, R. W. and Law, H. D. "J. Chem. Soc.", 7285 (1965). Aziridine 306 is then converted into the corresponding Boc derivative 307 by treatment with Boc anhydride. Such a conversion is described in Fitremann, J., et. al. "Tetrahedron Lett.", 35:1201 (1994).

The allylic aziridine 307 is opened selectively at the allylic position with a carbon nucleophile delivered via a higher order organocuprate in the presence of BF₃·Et₂O at low temperature to give the opened adduct 308. Such an opening is described in Hudlicky, T., et. al. "Synlett." 1125 (1995).

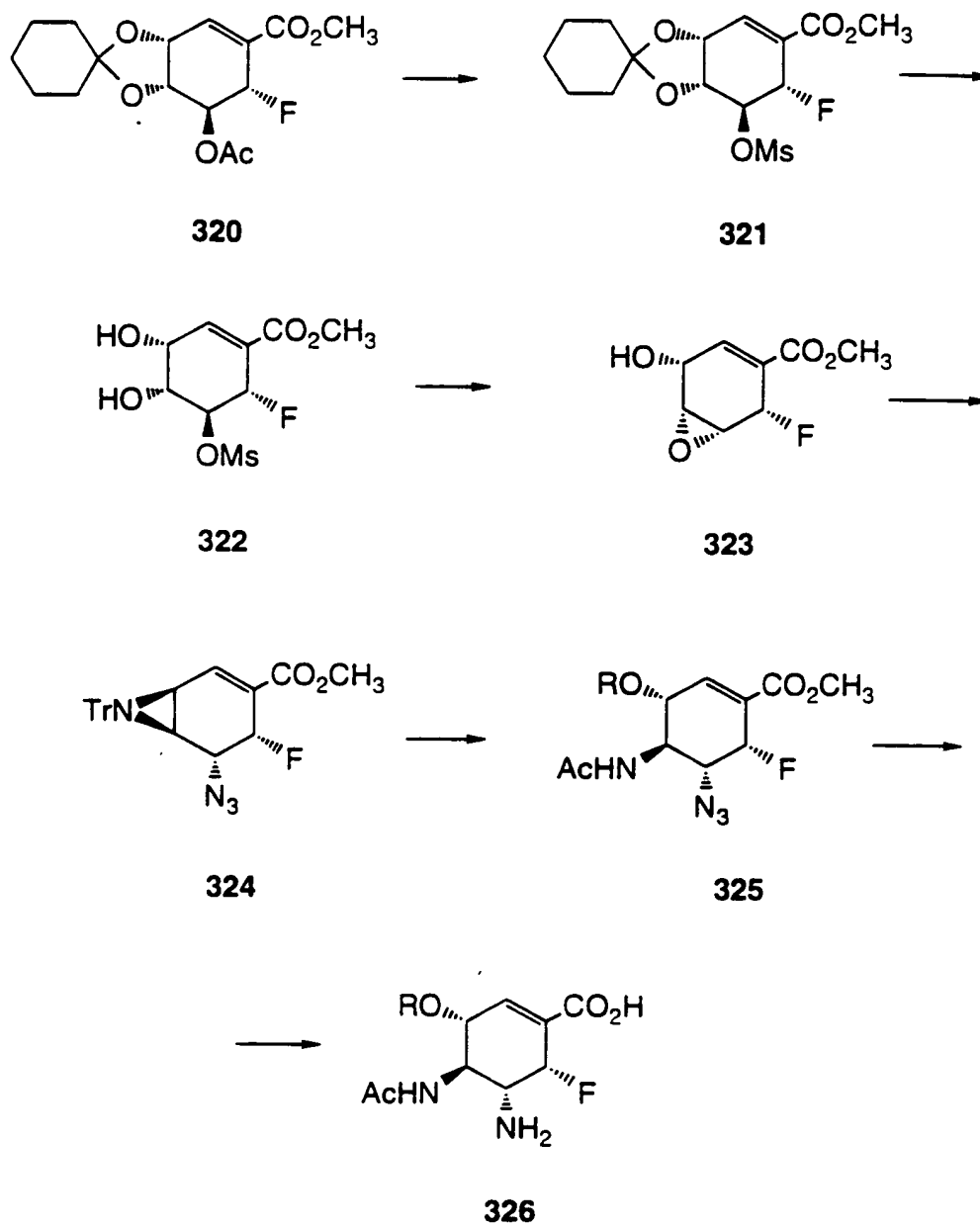
The Boc protected amine 308 is converted into the N-acetyl derivative 309 in a two step sequence: 1) TFA/CH₂Cl₂; 2) Ac₂O/pyridine. Such transformations can be found in Greene, T.W., "Protective Groups in Organic Synthesis", 2nd. Ed. (John Wiley & Sons, New York, 1991) pages 327-328 and pages 351-352.

Benzyl ether 309 is deprotected with DDQ at room temperature to give the primary allylic alcohol 310. Such a transformation is found in Horita, K., et. al. "Tetrahedron" 42:3021 (1986).

5 Alcohol 310 is oxidized and converted in a one pot reaction into the methyl ester 311 via a Corey oxidation using MnO₂/AcOH/MeOH/NaCN. Such a transformation can be found in Corey, E. J., et. al. "J. Am. Chem. Soc.", 90:5616 (1968).

10 Azido ester 311 is converted into amino acid 312 in a two step sequence 1) Ph₃P/H₂O/THF; 2) KOH/THF. Such a conversion has been described previously.

Scheme 42



Scheme 42

The known fluoro acetate **320** (Sutherland, J. K., et.al. "J. Chem. Soc. Chem. Commun." 464 (1993) is deprotected to the free alcohol and then converted into the corresponding mesylate **321** in two steps: 1) NaOMe; 2) MsCl/TEA. Such transformations are described in Greene, T.W., "Protective Groups in Organic Synthesis", 2nd. Ed. (John Wiley & Sons, New York, 1991).

Deprotection of **321** under acidic conditions gives diol **322** which is cyclized to the epoxy alcohol **323** under basic conditions. Such a conversion has been previously described.

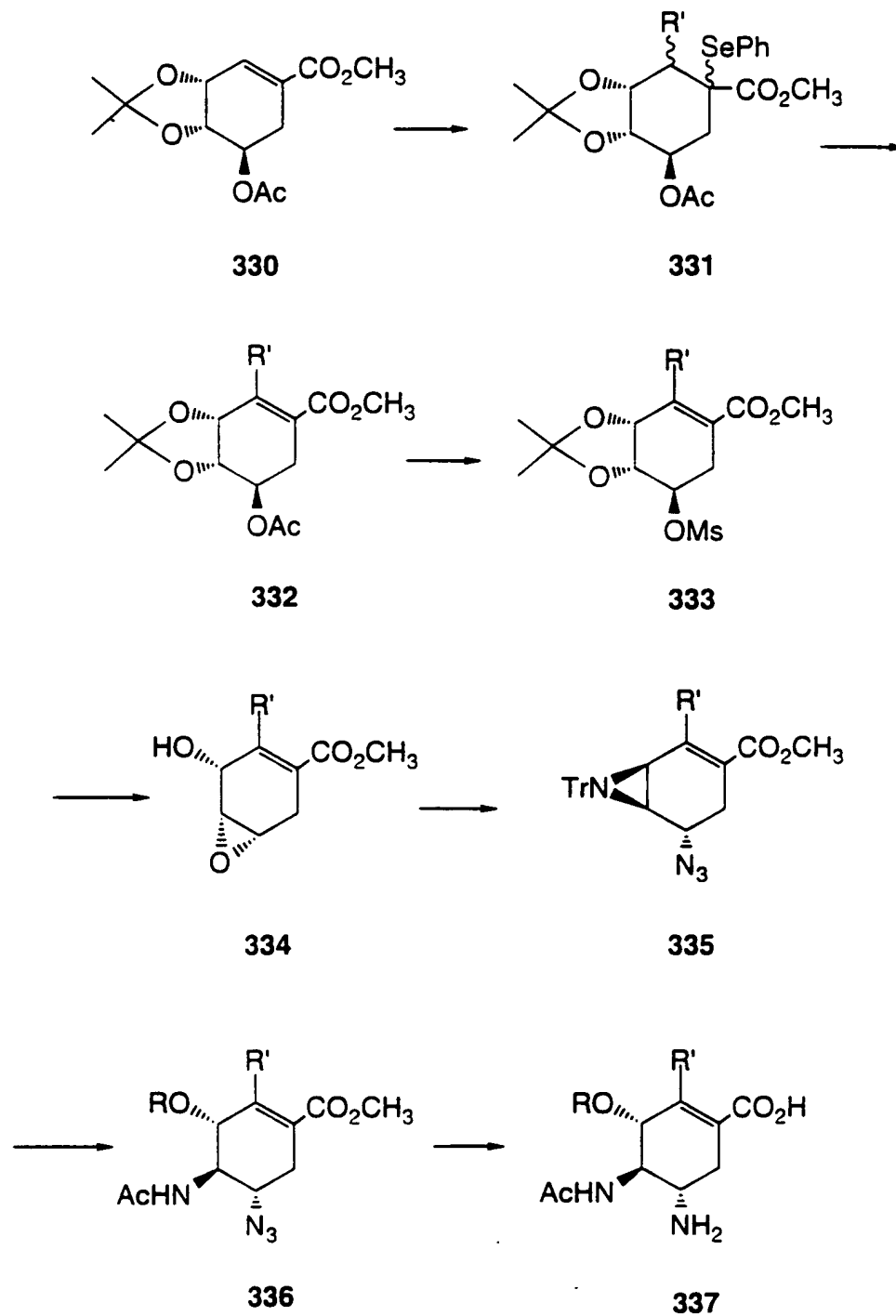
Conversion of **323** to the N-trityl protected aziridine **324** is accomplished with the following sequence: 1) MOMCl/TEA; 2) NaN₃/NH₄Cl; 3) MsCl/TEA; 4) PPh₃/TEA/H₂O; 5) NaN₃/NH₄Cl; 6) HCl/MeOH; 7) i) TrCl, ii) MsCl/TEA. Such a sequence has been previously described.

The aziridine **324** is then opened with the appropriate alcohol under Lewis acid conditions and then treated with Ac₂O/pyridine to give the acetylated product **325**. Such a transformation has been previously described.

The ester **325** is converted to the corresponding amino acid **326** in a two step sequence: 1) PPh₃/H₂O/THF; 2) KOH/THF. Such a transformation has been previously described.

United States Patent No. 5,214,165, and in particular, the "Descriptions and Examples" at column 9, line 61 to column 18, line 26, describes the preparation of 6 α and 6 β fluoro Shikimic acid. These fluoro compounds are suitable starting materials for methods of making compounds of the invention that use Shikimic acid.

Scheme 43



Scheme 43

Unsaturated ester 330 (obtainable by standard acetylation methods from the acetonide alcohol described in Campbell, M. M., et. al., "Synthesis", 179 (1993)) is reacted with the appropriate organocuprate where R' is the ligand to be transferred from the organocuprate. The resultant intermediate is then trapped with PhSeCl to give 331 which is then treated with 30% H₂O₂ to give the α,β -unsaturated ester 332. Such a transformation can be found in Hayashi, Y., et. al, "J. Org. Chem." 47:3428 (1982).

Acetate 332 is then converted into the corresponding mesylate 333 in a two step sequence: 1) NaOMe/MeOH; 2) MsCl/TEA. Such a transformation has been previously described and can also be found in Greene, T.W., "Protective Groups in Organic Synthesis", 2nd. Ed. (John Wiley & Sons, New York, 1991).

The acetonide 333 is then converted into the epoxy alcohol 334 in a two step sequence: 1) *p*-TsOH/MeOH/ Δ ; 2) DBU/THF. Such a transformation has been previously described.

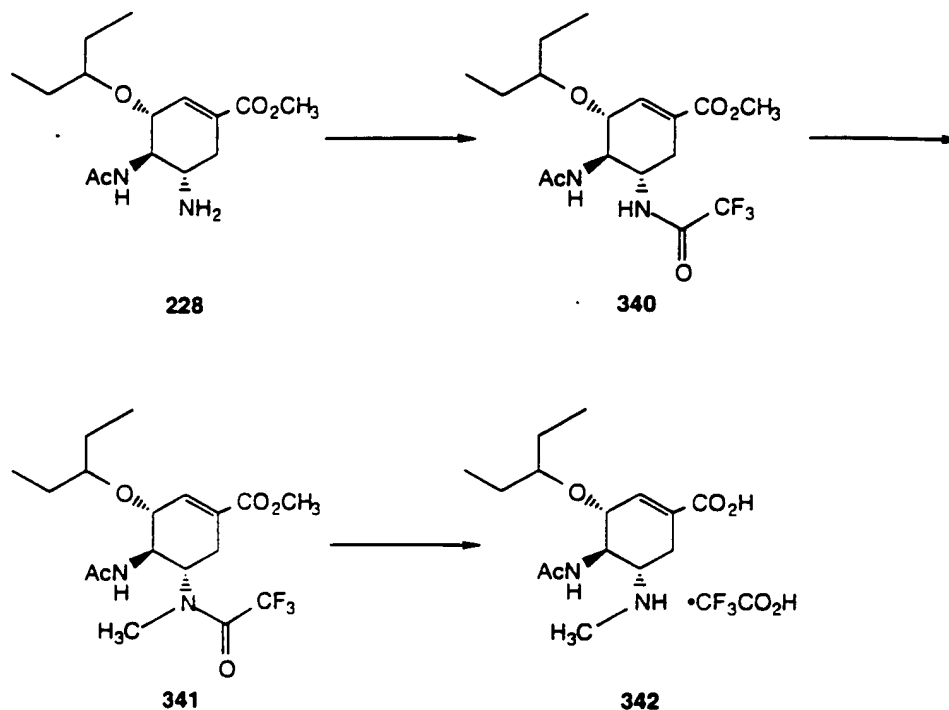
Conversion of epoxide 334 into N-trityl aziridine 335 is accomplished by the following sequence: 1) MOMCl/TEA; 2) NaN₃/NH₄Cl; 3) MsCl/TEA; 4) PPh₃/TEA/H₂O; 5) NaN₃/NH₄Cl; 6) HCl/MeOH; 7) i) TrCl, ii) MsCl/TEA. Such a sequence has been previously described.

The aziridine 335 is then opened with the appropriate alcohol under Lewis acid conditions and then treated with Ac₂O/pyridine to give the acetylated product 336. Such a transformation has been previously described.

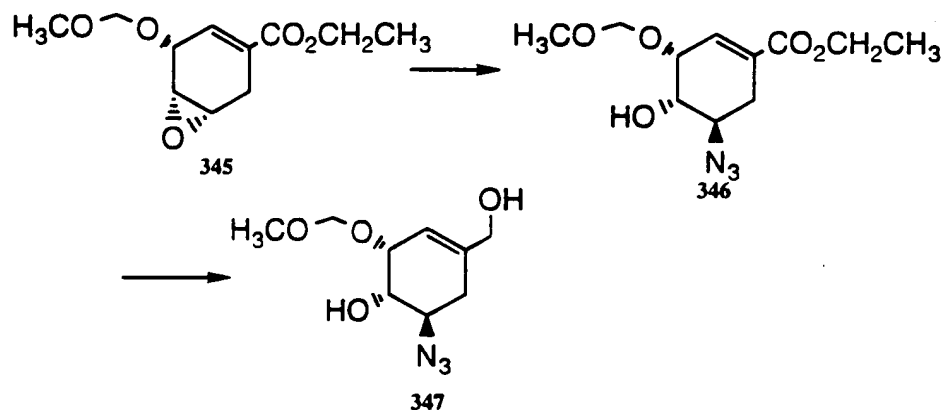
The azido ester 336 is converted to the corresponding amino acid 337 in a two step sequence: 1) PPh₃/H₂O/THF; 2) KOH/THF. Such a transformation has been previously described.

Schemes 44 and 45 are referred to in the examples.

Scheme 44



5 Scheme 45



Modification of the exemplary starting materials to form different E1 groups has been described in detail and will not be elaborated here. See Fleet, G.W.J. et al.; "J. Chem. Soc. Perkin Trans. I", 905-908 (1984), Fleet, G.W.J. et al.; "J. Chem. Soc., Chem. Commun.", 849-850 (1983), Yee, Ying K. et al.; "J. Med. Chem.", 33:2437-2451 (1990); Olson, R.E. et al.; "Bioorganic & Medicinal Chemistry Letters", 4(18):2229-2234 (1994); Santella, J.B. III et al.; "Bioorganic & Medicinal Chemistry Letters", 4(18):2235-2240 (1994); Judd, D.B. et al.; "J. Med.

Chem.", 37:3108-3120 (1994) and Lombaert, S. De et al.; "Bioorganic & Medicinal Chemistry Letters", 5(2):151-154 (1994).

The E1 sulfur analogs of the carboxylic acid compounds of the invention are prepared by any of the standard techniques. By way of example
5 and not limitation, the carboxylic acids are reduced to the alcohols by standard methods. The alcohols are converted to halides or sulfonic acid esters by standard methods and the resulting compounds are reacted with NaSH to produce the sulfide product. Such reactions are described in Patai, "The Chemistry of the Thiol Group" (John Wiley, New York, 1974), pt. 2, and in
10 particular pages 721-735.

Modifications of each of the above schemes leads to various analogs of the specific exemplary materials produced above. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

15 In each of the above exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase
20 extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or low pressure liquid chromatography, small scale and preparative thin or thick layer chromatography, as well as
25 techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular
30 sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

35 Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups

in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

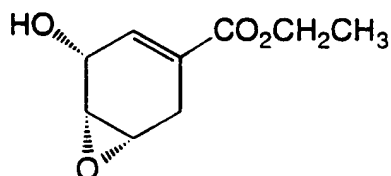
All literature and patent citations above are hereby expressly
5 incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following claims. It is apparent that certain modifications of the methods and
10 compositions of the following claims can be made within the scope and spirit of the invention.

Examples

General

15 The following Examples refer to the Schemes.

Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted
20 where the results varied significantly from those described. In Examples where different starting materials were used, these are noted. When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as
25 indicated. For example, the "corresponding ethyl ester of compound 1" is



500

Example 1

Epoxy alcohol 1: Prepared from shikimic acid by the procedure of
30 McGowan and Berchtold, "J. Org. Chem.", 46:2381 (1981).

Example 2

Epoxy allyl ether 2: To a solution of epoxy alcohol 1 (2.37g, 14.08 mmol) in dry benzene (50 mL) was added thallium(I)ethoxide (1.01 mL) in one portion. After 2 hr the reaction was concentrated *in vacuo* and the residue dissolved in acetonitrile. Allyl iodide (3.0 mL) was added and the mixture was stirred in the dark for 16 h. The solids were filtered thru a celite pad and washed with chloroform. Concentration *in vacuo* followed by flash chromatography (40% EtOAc in hexane) gave 1.24 g (42%) of 2 as a pale viscous oil. ¹H NMR (300 MHz, CDCl₃): δ 6.75 (1H, m); 6.10-5.90 (1H, m, -CH=, allyl); 5.40-5.15 (2H, m, =CH₂, allyl); 4.47-4.43 (1H, m); 4.30-4.15 (2H, m, -CH₂-, allyl); 3.73 (3H, s); 3.55-3.50 (1H, m); 3.45-3.40 (1H, m); 3.15-3.00 (1H, dm, *J* = 19.5 Hz), 2.50-2.35 (1H, dm, *J* = 2.7, 19.5 Hz).

Example 3

Azido alcohol 3: Epoxide 2 (1.17 g, 5.57 mmol), sodium azide (1.82 g) and ammonium chloride (658 mg) were refluxed in MeOH/H₂O (8:1) (35 mL) for 18 h. The reaction was then concentrated *in vacuo* and the residue partitioned between ethyl ether and water. The organic layer was washed with brine and dried. Concentration *in vacuo* gave 3 as a pale oil 1.3 g (92%) which was used without further purification. ¹H NMR (300 MHz, CDCl₃): δ 6.95-6.85 (1H, m); 6.00-5.85 (1H, m, -CH=, allyl); 5.35-5.25 (2H, m, =CH₂, allyl); 4.25-4.10 (2H, m, -CH₂-, allyl); 4.12 (1H, bt, *J* = 4.2 Hz); 3.95-3.75 (2H, m); 3.77 (3H, s); 2.85 (1H, dd, *J* = 5.3, 18.3 Hz); 2.71 (1H, bs); 2.26 (1H, dd, *J* = 7.2, 18.3 Hz).

Example 4

Aziridine 4: To a solution of alcohol 3 (637 mg, 2.52 mmol) in CH₂Cl₂ (20 mL) cooled to 0°C was added DMAP (few crystals) and triethyl amine (442 μL). MsCl (287 μL) was then added and the reaction stirred for 2 h at 0°C. Volatiles were removed and the residue partitioned between ethyl ether and water. The organic layer was washed with saturated bicarbonate, brine and then dried. Concentration *in vacuo* gave 881 mg of crude mesylate. ¹H NMR (300 MHz, CDCl₃): δ 6.87-6.84 (1H, s); 6.00-5.85 (1H, m, -CH=, allyl); 5.40-5.25 (2H, m, =CH₂, allyl); 4.72 (1H, dd, *J* = 3.9, 8.5 Hz); 4.32 (1H, bt, *J* = 3.9 Hz); 4.30-4.15 (2H, m, -CH₂-, allyl); 3.77 (3H, s); 3.14 (3H, s); 2.95 (1H, dd, *J* = 5.7, 18.6 Hz); 2.38 (1H, dd, *J* = 6.7, 18.6 Hz).

The crude mesylate was dissolved in dry THF (20 mL) and treated with Ph₃P (727 mg). After stirring for 3 h at room temperature, water (15 mL) and solid NaHCO₃ (1.35 g) was added and the mixture stirred overnight at room temperature. The reaction was then concentrated *in vacuo* and the residue partitioned between EtOAc, saturated bicarbonate and brine. The organic layer was separated and dried over MgSO₄. Concentration *in vacuo* and flash chromatography of the residue gave the aziridine 4 170 mg (33%) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 6.82-6.80 (1H, m); 6.04-5.85 (1H, m, -CH=, allyl); 5.35-5.20 (2H, m, =CH₂, allyl); 4.39 (1H, bd, *J* = 2.4 Hz); 4.20-4.05 (2H, m, -CH₂-allyl); 3.73 (3H, s); 2.90-2.80 (1H, bd, *J* = 18.9 Hz); 2.65-2.40 (2H, m).

Example 5

N-acetyl aziridine 5: Aziridine 4 (170 mg, 0.814 mmol) was dissolved in CH₂Cl₂ (2 mL) and pyridine (4 mL) and cooled to 0°C. Acetyl chloride (87 µL) was then added and the reaction stirred at 0°C for 1 h. Volatiles were removed *in vacuo* and the residue partitioned between ethyl ether, saturated bicarbonate and brine. The organic layer was separated and dried over MgSO₄. Concentration gave crude 5 196 mg (96%) which was used without further purification. ¹H NMR (300 MHz, CDCl₃): δ 6.88-6.86 (1H, m); 6.00-5.85 (1H, m, -CH=, allyl); 5.40-5.20 (2H, m, =CH₂, allyl); 4.45-4.40 (1H, m); 4.16 (2H, d, *J* = 6.0 Hz, -CH₂-, allyl); 3.76 (3H, s); 3.00-2.95 (2H, m); 2.65 (1H, bd, *J* = 18.5 Hz); 2.14 (3H, s).

Example 6

Azido allyl ether 6: Aziridine 5 (219 mg, 0.873 mmol), sodium azide (426 mg) and ammonium chloride (444 mg) in dry DMF (7 mL) was heated at 65°C under argon overnight. The reaction was poured into saturated bicarbonate/brine and extracted with ethyl ether several times. The combined ether layers were washed with brine and dried. Concentration followed by flash chromatography (EtOAc only) gave the azido amine 77 mg (35%) which was dissolved in CH₂Cl₂ (1 mL) and pyridine (1 mL) and cooled to 0°C. Acetyl chloride (38 µL) was added and after 45 min solid NaHCO₃ was added and the volatiles removed under vacuum. The residue was partitioned between EtOAc and brine. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography (EtOAc only) gave 6 90 mg (99%). ¹H NMR (500 MHz, CDCl₃): δ 6.86 (1H, bt, *J* = 2.2 Hz); 5.95-5.82 (1H, m, CH=, allyl); 5.68 (1H, bd, *J* = 7.3 Hz); 5.35-5.20 (2H, m, =CH₂, allyl); 4.58-4.52 (1H, m); 4.22-4.10

(2H, m); 4.04 (1H, dd, $J = 5.9, 12.5$ Hz); 3.77 (3H, s); 3.54-3.52 (1H, m); 2.89 (1H, dd, $J = 5.9, 17.6$ Hz); 2.32-2.22 (1H, m); 2.06 (3H, s).

Example 7

Azido diol 7: To a solution of olefin 6 (90 mg, 0.306 mmol) in acetone (3 ml) and water (258 μ L) was added N-methyl morpholine-N-oxide (39 mg) and OsO₄ (73 μ L of a 2.5 % w/w in *t*-butanol). The reaction was then stirred at room temperature for 3 days. Solid sodium hydrosulfite was added and after stirring for 20 min the reaction was filtered thru a celite pad and washed with copious amounts of acetone. Concentration *in vacuo* followed by flash chromatography (10% MeOH in CH₂Cl₂) gave the diol 7 50 mg (50%). ¹H NMR (300 MHz, CD₃CN): δ 6.80-6.70 (1H, m); 4.20-4.15 (1H, bm); 3.95-3.80 (1H, m); 3.80-3.25 (6H, m); 3.70 (3H, s); 3.10 (1H, bs); 2.85 (1H, bs); 2.85-2.75 (1H, m); 2.30-2.15 (1H, m); 2.16 (1H, bs); 1.92 (3H, s).

Example 8

Amino acid diol 8: A solution of the diol 7 (23 mg, 0.07 mmol) in THF (1 mL) was treated with aq. KOH (223 μ L, of 0.40 M solution) at room temperature. After stirring for 1.5 h the reaction was acidified to pH=4 with Amberlite IR-120 (plus) ion exchange resin. The resin was filtered and washed with MeOH. Concentration *in vacuo* gave the crude carboxylic acid which was dissolved in ethanol (1.5 mL). To this solution was added Lindlar's catalyst (20 mg) and the reaction stirred over a hydrogen atmosphere (1 atm via a balloon) for 20 h. The reaction mixture was filtered thru a celite pad and washed with hot ethanol and water. The ethanol was removed under vacuum and the resulting aqueous layer lyophilized to give a mixture of the desired amino acid 8 and the starting azide 7 as a white powder. Compound 8: ¹H NMR (500 MHz, D₂O): δ 6.5 (1H, s); 4.24-4.30 (2H, m); 4.25-4.18 (1H, m); 3.90-3.55 (5H, complex m); 2.96-2.90 (1H, m); 2.58-2.50 (1H, complex m); 2.12 (3H, s).

Example 9

Compound 62: A suspension of Quinic acid (60 g), cyclohexanone (160 mL) and toluenesulfonic acid (600 mg) in benzene (450 mL) was refluxed with Dean-Stark for 14 hrs. The reaction mixture was cooled to room temperature and poured into saturated NaHCO₃ solution (150 mL). The aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layers were washed with water (2x), brine (1x), and dried over Na₂SO₄. Concentration gave a whited

solid, which was recrystallized from ether (75 g, 95%): ^1H NMR (CDCl_3) δ 4.73 (dd, $J = 6.1, 2.5$ Hz, 1 H), 4.47 (ddd, $J = 7.0, 7.0, 3.0$ Hz, 1H), 4.30 (ddd, $J = 5.4, 2.6, 1.4$ Hz, 1 H), 2.96 (s, 1H), 2.66 (d, $J = 11.7$ Hz, 1H), 2.40-2.15 (m, 3 H), 1.72-1.40 (m, 10 H).

5 Example 10

Compound 63: To a solution of lactone 62 (12.7 g, 50 mmol) in methanol (300 mL) was added sodium methoxide (2.7 g, 50 mmol) in one portion. The mixture was stirred at room temperature for 3 hrs, and quenched with acetic acid (3 mL) and stirred for 10 min. The mixture was
10 poured into saturated NH_4Cl solution (300 mL), and extracted with CH_2Cl_2 (3x). The combined organic phase was washed with brine (1x), and dried over MgSO_4 . Purification by flash column chromatography (Hexane/EtOAc = 1/1 to 1/2) gave diol (11.5 g, 80%) and starting material (1.2 g, 10%): ^1H NMR (CDCl_3) δ 4.47 (ddd, $J = 7.4, 5.8, 3.5$ Hz, 1 H), 4.11 (m, 1 H), 3.98 (m, 1 H), 3.81 (s, 3
15 H), 3.45 (s, 1 H), 2.47 (d, $J = 3.3$ Hz, 1 H), 2.27 (m, 2 H), 2.10 (dd, $J = 11.8, 4.3$ Hz, 1 H), 1.92-1.26 (m, 10 H).

Example 11

Compound 64: To a mixture of diol 63 (1.100 g, 3.9 mmol), molecule sieves (3 A, 2.2 g) and pyridine (1.1 g) in CH_2Cl_2 (15 mL) was added PCC (3.3 g,
20 15.6 mmol) in one portion. The mixture was stirred at room temperature for 26 hrs, and diluted with ether (30 mL). The suspension was filtered through a pad of celite, and washed with ether (2x20 mL). The combined ether was washed with brine (2x), and dried over MgSO_4 . Concentration and purification was by flash column chromatography (Hexane/EtOAc = 3/1) gave
25 the ketone (0.690 g, 67%): ^1H NMR (CDCl_3) δ 6.84 (d, $J = 2.8$ Hz, 1 H), 4.69 (ddd, $J = 6.4, 4.9, 1.6$ Hz, 1 H), 4.30 (d, $J = 5.0$ Hz, 1 H), 3.86 (s, 3 H), 3.45 (d, $J = 22.3$ Hz, 1 H), 2.86 (m, 1 H), 1.69-1.34 (m, 10 H).

Example 12

Compound 28: To a solution of ketone 64 (0.630 g, 2.4 mmol) in MeOH
30 (12 mL) at 0°C was added NaBH_4 in 30 min. The mixture was stirred for additional 1.5 hrs at 0°C , and quenched with 15 mL of saturated NH_4Cl solution. The solution was extracted with CH_2Cl_2 (3x), and the combined organic extract was dried over MgSO_4 . Purification by flash column chromatography (Hexane/EtOAc = 2/1) gave the alcohol (0.614 g, 97%): ^1H
35 NMR (CDCl_3) δ 6.94 (d, $J = 0.5$ Hz, 1 H), 4.64 (ddd, $J = 9.8, 6.7, 3.2$ Hz, 1 H), 4.55

(dd, $J = 7.1, 4.2$ Hz, 1 H), 4.06 (m, 1 H), 3.77 (s, 3 H), 3.04 (dd, $J = 16.5, 2.1$ Hz, 1 H), 2.73 (d, $J = 10.2$ Hz, 1 H), 1.94 (m, 1 H), 1.65-1.29 (m, 10 H).

Example 13

Compound 66: Alcohol 28 (2.93 g, 10.9 mmol) and toluenesulfonic acid (1.5 g) were dissolved in acetone (75 mL), and the mixture was stirred at room temperature for 15 hrs. The reaction was quenched with water (30 mL), and basified with concentrated $\text{NH}_3\text{-H}_2\text{O}$ until $\text{PH} = 9$. Acetone was removed under reduced pressure, and the water phase was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine (1x), and dried over Na_2SO_4 . Concentration gave the desired product: ^1H NMR (CDCl_3) δ 7.01 (m, 1 H), 4.73 (m, 1 H), 4.42 (m, 1 H), 3.97 (m, 1 H), 3.76 (s, 3 H), 2.71-2.27 (m, 2 H), 2.02 (s, 3 H), 1.98 (s, 3 H).

Example 14

Compound 67: To a solution of alcohol 66 (10.9 mmol) in CH_2Cl_2 (60 mL) at 0°C was added pyridine (4.4 mL, 54.5 mmol), followed by addition of trimethylacetyl chloride (2.7 mL, 21.8 mmol). The mixture was warmed to room temperature and stirred for 14 hrs. The mixture was diluted with CH_2Cl_2 , and washed with water (2x), brine (1x), and dried over MgSO_4 . Purification by flash column chromatography (Hexane/ $\text{EtOAc} = 9/1$) gave the diester (2.320 g, 68%): ^1H NMR (CDCl_3) δ 6.72 (m, 1 H), 5.04 (m, 1 H), 4.76 (m, 1 H), 4.40 (m, 1 H), 3.77 (s, 3 H), 2.72-2.49 (m, 2 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.23 (s, 9 H).

Example 15

Compound 68: Diester 67 (2.32 g, 2.3 mmol) was dissolved in acetone/ H_2O (1/1, 100 mL) and heated at 55°C for 16 hrs. Solvents were removed, water (2 x 50 mL) was added and evaporated. Concentration with toluene (2 x 50 mL) gave diol, which was used without further purification: ^1H NMR (CDCl_3) δ 6.83 (m, 1 H), 5.06 (m, 1 H), 4.42 (m, 1 H), 4.09 (m, 1 H), 3.77 (s, 3 H), 2.68-2.41 (m, 2 H), 1.22 (s, 9 H).

Example 16

Compound 69: To a solution of diol 68 (0.410 g, 1.5 mmol) in THF (8 mL) at 0°C was added triethylamine (0.83 mL, 6.0 mmol), followed by slow addition of thionyl chloride (0.33 mL, 4.5 mmol). The mixture was warmed to room temperature and stirred for 3 hrs. The mixture was diluted with CHCl_3 , and washed with water (3x), brine (1x), and dried over MgSO_4 . Purification by

flash column chromatography (Hexanes/EtOAc = 5/1) gave a exo/endo mixture (0.430 g, 90%): ^1H NMR (CDCl_3) δ 6.89-6.85 (m, 1 H), 5.48-4.84 (m, 3 H), 3.80, 3.78 (s, 3 H), 2.90-2.60 (m, 2 H), 1.25, 1.19 (s, 9 H).

Example 17

5 **Compound 70:** The mixture of sulfone **69** (0.400 g, 1.3 mmol) and sodium azide (0.410 g, 6.29 mmol) in DMF (10 mL) was stirred for 20 hrs. The reaction mixture was then diluted with ethyl acetate, washed with saturated NH_4Cl solution, water, brine, and dried over MgSO_4 . Concentration gave the azide (0.338 g, 90%): ^1H NMR (CDCl_3) δ 6.78 (m, 1 H), 5.32 (m, 1 H), 4.20 (m, 1 H), 3.89 (m, 1 H), 3.78 (s, 3 H), 3.00-2.60 (m, 2 H), 1.21 (s, 9 H).
10

Example 18

Compound 71: To a solution of alcohol **70** (0.338 g, 1.1 mmol) in CH_2Cl_2 (11 mL) at 0°C was added triethylamine (0.4 mL, 2.9 mmol), followed by slow addition of methylsulfonic chloride (0.18 mL, 2.3 mmol). The mixture was stirred at 0°C for 30 min., and diluted with CH_2Cl_2 . The organic layer was washed with water (2x), brine, and dried over MgSO_4 . Purification by flash column chromatography (Hexane/EtOAc = 3/1) gave the desired compound (0.380 g, 82%): ^1H NMR (CDCl_3) δ 6.82 (m, 1 H), 5.44 (m, 1 H), 4.76 (dd, $J = 7.3, 1.4$ Hz, 1 H), 4.48 (m, 1 H), 3.80 (s, 3 H), 3.11 (s, 3 H), 2.82-2.61 (m, 2 H), 1.21 (s, 9 H).
15
20

Example 19

Compound 72: The mixture of azide **71** (0.380 g, 0.94 mmol) and triphenylphosphine (0.271 g, 1.04 mmol) in THF (19 mL) was stirred for 2 hrs. The reaction was quenched with water (1.9 mL) and triethylamine (0.39 mL, 2.82 mmol), and the mixture was stirred for 14 hrs. Solvents were removed under reduced pressure, and the mixture was used for next step. To a solution of above mixture in CH_2Cl_2 (20 mL) at 0°C was added pyridine (0.68 mL, 8.4 mmol), followed by slow addition of acetyl chloride (0.30 mL, 4.2 mmol). The mixture was stirred at 0°C for 5 min., and diluted with ethyl acetate. The mixture was washed with water (2x), brine (1x), dried over MgSO_4 . Purification by flash column chromatography (Hexanes/EtOAc = 3/1) gave the aziridine (0.205 g, 83%): ^1H NMR (CDCl_3) δ 7.19 (m, 1 H), 5.58 (m, 1 H), 3.77 (s, 3 H), 3.14 (m, 2 H), 2.85 (dd, $J = 7.0, 1.6$ Hz, 1 H), 2.34 (m, 1 H), 2.16 (s, 3 H), 1.14 (s, 9 H).
25
30

Example 20

Compound 73: The mixture of aziridine 72 (0.200 g, 0.68 mmol), sodium azide (0.221 g, 3.4 mmol), and ammonium chloride (0.146 g, 2.7 mmol) in DMF (10 mL) was stirred at room temperature for 14 hrs. Then the mixture was diluted with ethyl acetate, and washed with water (5x), brine (1x), and dried over MgSO₄. Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave desired product and deacetyl amine (0.139 g). The mixture was dissolved in acetic anhydride (2 mL), and stirred for 2 hrs. Excess anhydride was removed under reduced pressure, and give the desired product (149 mg): ¹H NMR (CDCl₃) δ 6.76 (m, 1 H), 5.53 (d, J = 8.5 Hz, 1 H), 5.05 (m, 1 H), 4.31 (m, 1 H), 4.08 (m, 1 H), 3.79 (s, 3 H), 2.91 (m, 1 H), 2.51 (m, 1 H), 1.99 (s, 3 H), 1.20 (s, 9 H).

Example 21

Compound 74: A solution of potassium hydroxide in MeOH/H₂O (0.5 M, 4.4 mL, 2.2 mmol) was added to ester 73 (149 mg, 0.44 mmol) and the mixture was stirred at room temperature for 3 hrs. The mixture was cooled to 0°C, and acidified with Amberlite (acidic) to PH = 3-4. The mixture was filtered, and washed with MeOH. Concentration gave the carboxylic acid as a white solid (73 mg, 69%): ¹H NMR (CD₃OD) δ 6.62 (m, 1 H), 4.15 (m, 1 H), 3.95-3.72 (m, 2 H), 2.84 (dd, J = 6.7, 1.4 Hz, 1 H), 2.23 (m, 1 H), 1.99 (s, 3 H).

Example 22

Compound 75: The mixture of azide 74 (8 mg) and Pd-C (Lindlar) (15 mg) in ethanol (2 mL) was stirred under hydrogen for 16 hrs. The mixture was filtered through celite, washed with hot MeOH-H₂O (1/1). Concentration gave a solid. The solid was dissolved in water, and passed through a short C-8 column, and washed with water. Concentration gave a white solid (6 mg): ¹H NMR (D₂O) δ 6.28 (m, 1 H), 4.06-3.85 (m, 3 H), 2.83 (dd, J = 17.7, 5.4 Hz, 1 H), 2.35 (m, 1 H), 2.06 (s, 3 H).

Example 23

Compound 76: Carboxylic acid 74 (68 mg, 0.28 mmol) and diphenyldiazomethane (61 mg, 0.31 mmol) were dissolved in ethanol (12 mL), and stirred for 16 hrs. The reaction was quenched with acetic acid (0.5 mL), and the mixture was stirred for 10 min. Solvents were removed under reduced pressure. Purification by flash column chromatography (EtOAc) gave

the ester (56 mg, 50%): ^1H NMR (CD_3OD) δ 7.36-7.23 (m, 10 H), 6.88 (s, 1 H), 6.76 (s, 1 H), 4.21 (m, 1 H), 3.93-3.79 (m, 2 H), 2.89 (dd, J = 17.7, 5.0 Hz, 1 H), 2.34 (m, 1 H), 2.00 (s, 3 H).

Example 24

5 **Compound 77:** To a solution of alcohol 76 (20 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added pyridine (40 μL , 0.5 mmol), followed by addition of acetic anhydride (24 μL , 0.25 mmol). The mixture was stirred for 24 hrs, and solvents and reagents were removed under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 1/2) gave the diester (20 mg,
10 91%): ^1H NMR (CDCl_3) δ 7.40-7.27 (m, 10 H), 6.95 (s, 1 H), 6.87 (m, 1 H), 5.60 (m, 1 H), 5.12 (ddd, J = 16.4, 10.2, 5.9 Hz, 1 H), 4.28 (dd, J = 20.0, 9.4 Hz, 1 H), 4.15 (m, 1 H), 2.93 (dd, J = 17.8, 5.2 Hz, 1 H), 2.57 (m, 1 H), 2.09 (s, 3 H), 2.01 (s, 3 H).

Example 25

15 **Compound 78:** The mixture of diester 77 (20 mg, 0.045 mmol), anisole (50 μL , 0.45 mmol), and TFA (1 mL) in CH_2Cl_2 (1 mL) was stirred for 20 min. Solvents and reagents were removed under reduced pressure. Purification by flash column chromatography (EtOAc to EtOAc/AcOH = 100/1) gave the carboxylic acid (6 mg): ^1H NMR (CDCl_3) δ 6.85 (m, 1 H), 5.54 (m, 1 H), 5.12 (m,
20 1 H), 4.31-4.03 (m, 2 H), 2.89 (m, 1 H), 2.60-2.41 (m, 1 H), 2.11 (s, 3 H), 2.03 (s, 3 H).

Example 26

25 **Compound 79:** The mixture of azide 78 (6 mg, 0.02 mmol) and Pd-C (Lindlar) (15 mg) in EtOH/ H_2O (2.2 mL, 10/1) was stirred under hydrogen for 3 hrs. The mixture was filtered through a pad of celite, washed with hot MeOH/ H_2O (1/1). Evaporation gave a white solid. The solid was dissolved
in water, and passed through a C-8 column. Evaporation of water gave a white powder (3 mg): ^1H NMR (D_2O) δ 6.32 (m, 1 H), 5.06 (m, 1 H), 4.06 (t, J = 10.4 Hz, 1 H), 3.84 (m, 1 H), 2.83 (m, 1 H), 2.42 (m, 1 H), 2.06 (s, 3 H), 2.00 (s, 3 H).

Example 27

30 **Compound 80:** To a solution of alcohol 76 (35 mg, 0.086 mmol), Boc-glycine (30 mg, 0.172 mmol), and catalytic amount DMAP in CH_2Cl_2 (1 mL) was added DCC (35 mg, 0.172 mmol). The mixture was stirred for 30 min, and filtered and washed with CHCl_3 . The CHCl_3 solution was washed with water (2x). Concentration gave a white solid. Purification by flash column
35 chromatography (Hexane/EtOAc = 1/2) gave product (30 mg): ^1H NMR

(CDCl₃) δ 7.39-7.26 (m, 10 H), 6.95 (s, 1 H), 6.86 (m, 1 H), 5.77 (m, 1 H), 5.27 (m, 1 H), 4.99 (m, 1 H), 4.18-4.01 (m, 2 H), 3.94-3.84 (m, 2 H), 2.96 (dd, J = 7.8, 5.9 Hz, 1 H), 2.57 (m, 1 H), 2.02 (s, 3 H), 1.45 (s, 9 H).

Example 28

5 **Compound 81:** The mixture of diester 80 (30 mg, 0.05 mmol), anisole (150 μL), and TFA (1 mL) in CH₂Cl₂ (1 mL) was stirred for 3 hrs. Solvents and reagents were evaporated. The mixture was dissolved in water, and washed with CHCl₃ (3x). Water phase was evaporated to give a white solid (15 mg):
10 ¹H NMR (CD₃OD) δ 6.73 (m, 1 H), 5.25-5.15 (m, 1 H), 4.35 (m, 1 H), 4.17 (m, 1 H), 3.82 (m, 2 H), 2.93 (dd, J = 17.7, 5.6 Hz, 1 H), 2.42 (m, 1 H), 1.97 (s, 3 H).

Example 29

15 **Compound 82:** The mixture of azide 81 (15 mg, 0.05 mmol) and Pd-C (Lindlar) (30 mg) in EtOH/H₂O (4 mL, 1/1) was stirred under hydrogen for 3 hrs. The mixture was filtered through a pad of celite, and washed with hot MeOH/H₂O (1/1). Concentration gave a glass-like solid. The solid was
dissolved in water, and passed through C-8 column. Evaporation of water gave the amino acid: ¹H NMR (D₂O) δ 6.68 (m, 1 H), 5.28 (m, 1 H), 4.29 (m, 1 H), 4.08-3.79 (m, 3 H), 2.85 (m, 1 H), 2.41 (m, 1 H), 2.04 (s, 3 H).

Example 30

20 **bis-Boc guanidiny methyl ester 92:** Treated according to the procedure of Kim and Qian, "Tetrahedron Lett.", 34:7677 (1993). To a solution of amine 91 (42 mg, 0.154 mmol), bis-Boc thiourea (43 mg, 0.155 mmol) and triethylamine (72 μL) in dry DMF (310 μL) cooled to 0°C was added mercury chloride (46 mg, 0.170 mmol) in one portion. After 30 min the reaction was
25 warmed to room temperature and stirred for an additional 2.5 h. The reaction mixture was then filtered through a celite pad, concentrated and purified by flash column chromatography (100% ethyl acetate) to give 70 mg (89%) of 92 as a colorless foam. ¹H NMR (CDCl₃, 300 MHz): δ 11.37 (s, 1H); 8.60 (d, 1H, J = 7.8 Hz); 6.83 (t, 1H, J = 2.1 Hz); 6.63 (d, 1H, J = 8.4 Hz); 4.76 (d, 1H, J = 7.0 Hz);
30 4.71 (d, 1H, J = 7.0 Hz); 4.45-4.10 (complex m, 2H); 3.76 (s, 3H); 3.39 (s, 3H); 2.84 (dd, 1H, J = 5.4, 17.4 Hz); 2.45-2.30 (m, 1H); 1.92 (s, 3H); 1.49 (s, 18H).

Example 31

35 **bis-Boc guanidiny carboxylic acid 93:** To a solution of ester 92 (70 mg, 0.136 mmol) in THF (3 mL) cooled to 0°C was added aq. KOH (350 μL of a 0.476 M solution). The reaction was then warmed to room temperature and stirred

for 2 h. The reaction was then acidified to pH = 4.5 with Amberlite IR-120 (plus) acidic resin. The resin was then filtered and washed with ethanol and H₂O. Concentration *in vacuo* gave 66 mg (97%) of carboxylic acid 93 as a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 11.40 (br s, 1H); 8.67 (d, 1H, *J* = 7.8 Hz); 6.89 (s, 1H); 6.69 (br d, 1H, *J* = 8.4 Hz); 4.77 (d, 1H, *J* = 7.2 Hz); 4.70 (d, 1H, *J* = 7.2 Hz); 4.40-4.15 (m, 2H); 3.39 (s, 3H); 2.84 (dd, 1H, *J* = 4.8, 17.1 Hz); 2.45-2.30 (m, 1H); 1.95 (s, 3H); 1.49 (s, 9H); 1.48 (s, 9H).

Example 32

Guanidine carboxylic acid TFA salt 94: To a solution of bis-Boc guanidiny carboxylic acid 93 (23 mg, 0.046 mmol) in CH₂Cl₂ (1 mL) cooled to 0°C was added neat trifluoroacetic acid (500 μL). After 30 min the reaction was warmed to room temperature and stirred for an additional 1.25 h. Volatiles were removed under vacuum and the residue co-evaporated with several portions of H₂O to give a pale orange solid. The residue was purified by reverse phase C₁₈ chromatography using H₂O as an eluent. Fractions containing the desired product were pooled and lyophilized to give 15 mg of 93 as a white powder. ¹H NMR (D₂O, 500 MHz): δ 6.82 (t, 1H, *J* = 2.0 Hz); 4.51-4.47 (m, 1H); 3.93 (dd, 1H, *J* = 9.0, 11.2 Hz); 3.87-3.80 (apparent ddd, 1H); 2.88 (m, 1H); 2.48-2.45 (complex m); 2.07 (s, 3H). ¹³C NMR (D₂O): δ 176.1; 170.0; 157.1; 139.2; 129.5; 69.4; 56.2; 50.9; 30.3; 22.2.

Example 33

Synthesis of 102: A solution of azido allyl ether 6 (24 mg, 0.082 mmol) in ethanol (1 mL) was treated with hydrogen gas (1 atm) over Lindlar's catalyst (30 mg) for 1.5 h. The reaction mixture was filtered through a celite pad and washed with hot ethanol. Concentration *in vacuo* gave a pale solid which was dissolved in THF (1.5 mL) and treated with aqueous KOH (246 μL of a 0.50 M solution). After stirring at ambient temperature for 2 h the reaction was acidified to pH = 4.0 with Amberlite IR-120 (plus) acidic resin, filtered and washed with ethanol and H₂O. Concentration *in vacuo* gave an orange solid which was purified by a C₁₈ column chromatography eluting with H₂O. Fractions containing the product were pooled and lyophilized to give a 2 to 1 mixture of 102 and the fully saturated compound 103 as a white powder. ¹H NMR data for compound 102: ¹H NMR (D₂O, 500 MHz): δ: 7.85 (s, 1H); 4.29 (br d, 1H, *J* = 9.2 Hz); 4.16 (dd, 1H, *J* = 11.6, 11.6 Hz); 3.78 - 3.72 (m, 2H); 3.62 (apparent ddd, 1H); 2.95 (apparent dd, 1H); 2.58 - 2.52 (m, 1H); 2.11 (s, 3H); 1.58 (q, 2H, *J* = 7.3 Hz); 0.91 (t, 3H, *J* = 7.3 Hz).

Example 34

Synthesis of 115: A solution of amino acid 114 (10.7 mg, 0.038 mmol) in water (1.3 mL) cooled to 0°C was adjusted to pH = 9.0 with 1.0 M NaOH.

Benzyl formimidate hydrochloride (26 mg, 0.153 mmol) was then added in one portion and the reaction stirred between 0 - 5°C for 3 h while maintaining the pH between 8.5 - 9.0 with 1.0 M NaOH. The reaction was then concentrated *in vacuo* and the residue applied to a C₁₈ column and eluted with water. Fractions containing the product were pooled and lyophilized to give the formamidine carboxylic acid 115 (10 mg) as a white powder. ¹H NMR (D₂O, 300 MHz, mixture isomers): δ 7.83 (s, 1H); [6.46(s) & 6.43 (s); 1 H total]; 4.83 (d, 1H, J = 7.3 Hz); 4.73 (d, 1H, J = 7.3 Hz); 4.50 - 4.35 (m, 1H); 4.10 - 4.05 (m, 1H); [4.03 - 3.95 (m) & 3.80 - 3.65 (m), 1 H total]; 3.39 (s, 3H); 2.90 - 2.75 (m, 1H); 2.55 - 2.30 (m, 1H); [2.03 (s) & 2.01 (s), 3H total].

Example 35

Compound 123: To a solution of alcohol 63 (5.842 g, 20.5 mmol) and DMAP (200 mg) in pyridine (40 mL) was added tosyl chloride (4.3 g, 22.6 mmol). The mixture was stirred at room temperature for 40 hrs, and pyridine was removed under reduced pressure. The reaction was quenched with water, and extracted with EtOAc (3x). The combined organic extracts were washed with water, brine, and dried over MgSO₄. Purification by flash column chromatography (Hexanes/EtOAc = 2/1) gave the tosylate (8.04 g, 89%): ¹H NMR (CDCl₃) δ 7.84 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 4.78 (m, 1 H), 4.43 (m, 1 H), 4.06 (m, 1 H), 3.79 (s, 3 H), 2.44 (s, 3 H), 2.43-1.92 (m, 4 H), 1.61-1.22 (m, 10 H).

Example 36

Compound 124: To a solution of alcohol 123 (440 mg, 1.0 mmol) in pyridine (3 mL) was added POCl₃ (100 μL, 1.1 mmol). The mixture was stirred at room temperature for 12 hrs, and quenched with saturated NH₄Cl solution. The water phase was extracted with ether (3x). The combined ether layers were washed with water (2x), 2 N HCl solution (2x), brine, and dried over MgSO₄. Purification by flash column chromatography (Hexane/EtOAc = 2/1) gave a mixture of the desired product 124 and some impurity (350 mg, 83%, 2/1).

Example 37

Compound 1: To a solution of the known acetonide of methyl shikimate (877 mg, 3.85 mmol, "Tetrahedron Lett.", 26:21 (1985)) in dichloromethane (15 mL) at -10°C was added methanesulfonyl chloride (330 µL, 4.23 mmol) followed by the dropwise addition of triethylamine (640 µL, 4.62 mmol). The solution was stirred at -10°C for 1 h then at 0°C for 2 h, at which time methanesulfonyl chloride (30 µL), triethylamine (64 µL) was added. After 1 h cold water was added, the organic phase was separated, washed with water, dried (MgSO₄), and evaporated. The crude product was chromatographed on silica gel (1/1-hexane/ethyl acetate) to provide mesylate **130** (1.1 g, 93%) as an oil. Mesylate **130** (990 mg, 3.2 mmol) was dissolved in tetrahydrofuran (5 mL) and was treated with 1M HCl (5 mL). The solution was stirred at room temperature for 19 h, diluted with water (5 mL) and stirred an additional 7 h. Evaporation of the organic solvent precipitated an oily residue which was extracted into ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated. Addition of CH₂Cl₂ to the crude residue precipitated a white solid which was filtered and washed with CH₂Cl₂ to afford diol **131** (323 mg, 38%). To a partial suspension of diol **131** (260 mg, 0.98 mmol) in THF (5 mL) at 0°C was added DBU (154 µL, 1.03 mmol). The solution was stirred at 0°C for 3 h and then was warmed to room temperature stirring for 5 h. The solvent was evaporated and the crude residue was partitioned between ethyl acetate (40 mL) and 5% citric acid (20 mL). The organic phase was washed with brine. Aqueous phases were back extracted with ethyl acetate (15 mL) and the combined organic extracts were dried (MgSO₄) and evaporated to afford the epoxide (117 mg, 70%) as a white solid which gave an ¹H NMR spectrum consistent with structure **1** prepared by literature method.

Example 38

Alcohol 51: To a solution of protected alcohol (PG=methoxymethyl) (342 mg, 1.15 mmol) in CH₂Cl₂ (10 mL) at 0°C was added trifluoroacetic acid (8 mL). After 5 min at 0°C, the solution was stirred 1 h at room temperature and was evaporated. The crude product was purified on silica gel (ethyl acetate) to afford alcohol **51** (237 mg, 82%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 2.11 (s,

3H), 2.45 (m, 1H), 2.97 (dd, 1H, $J = 3.8, 18.8$), 3.66 (m, 2H), 3.78 (s, 3H), 4.40 (br s, 1H), 5.22 (br s, 1H), 6.19 (br s, 1H), 6.82 (m, 1H).

Example 39

Methyl ether 150: To a solution of alcohol 51 (46 mg, 0.18 mmol) and methyl iodide (56 μ L, 0.90 mmol) in THF (0.7 mL) at 0°C was added NaH as a 60% mineral oil dispersion (8 mg, 0.20 mmol). The solution was stirred at 0°C for 2.5 h, and a second portion of NaH (2 mg) was added. After an additional 1 h at 0°C and 4 h at room temperature the solution was cooled to 0°C and 5% citric acid (0.5 mL) was added. The mixture was extracted with ethyl acetate (4X2mL) and the combined organic extracts were dried (MgSO₄), and evaporated. Purification of the crude residue on silica gel (ethyl acetate) gave methyl ether 150 (12 mg, 25%) as a solid: ¹H NMR (300 MHz, CDCl₃) δ 2.07 (s, 3H), 2.23-2.34 (m, 1H), 2.89 (app ddd, 1H), 3.43 (s, 3H), 3.58 (m, 1H), 3.78 (s, 3H), 4.13 (m, 1H), 4.40 (m, 1H), 5.73 (d, 1H, $J = 7.6$), 6.89 (m, 1H).

Example 40

Amino acid 151: To a solution of methyl ether 150 (12 mg, 0.45 mmol) in THF(1 mL)/water (100 μ L) was added polymer support Ph₃P (75 mg, 3 mmol P/g resin). The mixture was stirred at room temperature for 19 h. The resin was filtered, washed several times with THF and the combined filtrate and washings were evaporated to provide 8 mg of a crude residue. The residue was dissolved in THF (0.5 mL), and 0.5 M KOH (132 μ L)/water (250 μ L) was added. The solution was stirred at room temperature for 1.25 h and the pH was adjusted to 3-4 with IR120 ion exchange resin. The resin was filtered and was stirred with 1M HCl. After filtration, the resin was subjected to the same treatment with 1M HCl until the acidic washes no longer tested positive for amine with ninhydrin. The combined resin washings were evaporated and the residue was purified on C-18 reverse phase silica eluting with water to afford after lyophilization, amino acid 151 (1.8 mg, 15%) as a white solid: ¹H NMR (300 MHz, D₂O) δ 2.09 (s, 3H), 2.48-2.59 (app qt, 1H), 2.94 (dd, 1H, $J = 5.7, 17.4$), 3.61 (m, 1H), 4.14-4.26 (m, 2H), 6.86 (br s, 1H).

Example 41

Amino acid allyl ether 153: To a solution of azide 6 (16 mg, 0.054 mmol) in THF (0.50 mL) and H₂O (35 μ L) was added polystyrene supported PPh₃ (50 mg). The reaction was stirred at ambient temperature for 24 h, filtered through a sintered glass funnel and washed with hot methanol.

Concentration *in vacuo* gave the crude amino ester which was dissolved in THF (1.0 mL) and treated with aqueous KOH (220 μ L of a 0.5 M solution). After stirring at ambient temperature for 2 h Amberlite IR-120 (plus) acidic resin was added until the solution attained pH = 4.5. The resin was filtered
5 and washed with ethanol and H₂O. Concentration *in vacuo* gave a pale orange solid which was purified by reverse phase C₁₈ chromatography using H₂O as an eluent. Fractions containing the desired product were pooled and lyophilized to give the amino acid as a white powder. ¹H NMR (D₂O, 300 MHz): δ 6.51 (br t, 1H); 6.05-5.80 (m, 1H, -CH=, allyl); 5.36-5.24 (m, 2H, =CH₂, allyl); 4.35-4.25 (m, 1H); 4.25 - 4.05 (m, 2H, -CH₂-, allyl); 4.02-3.95 (m, 1H); 3.81-3.70 (m, 1H); 2.86-2.77 (apparent dd, 1H); 2.35-2.24 (complex m, 1H); 2.09 (s, 3H).

Example 42

Epoxide 161: MCPBA (690 mg) was added to a solution of olefin 160 (532 mg, 1.61 mmol, prepared by Example 14, crude mesylate was filtered
15 through silica gel using 30% EtOAc/Hexanes prior to use) in dichloromethane (15 mL) cooled to 0°C. The mixture was warmed to room temperature and stirred overnight. The bulk of the solvent was removed under vacuum and the mixture diluted with ethyl acetate. The organic layer was washed with aqueous sodium bisulfite, saturated sodium bicarbonate, brine and dried over
20 MgSO₄. Concentration *in vacuo* followed by flash column chromatography of the residue (30% hexanes in ethyl acetate) gave 437 mg (78%) of 161 as a pale oil. ¹H NMR (CDCl₃, 300 MHz): [1:1 mixture of diastereomers] δ [4.75 (dd, *J* = 3.9, 8.2 Hz) & 4.71 (dd, *J* = 3.9, 8.4 Hz), 1H total]; 4.37 (m, 1H); 4.25-4.00 (m, 2H); 3.78 (s, 3H); [3.68 (dd, *J* = 5.7, 11.7 Hz) & 3.51 (dd, *J* = 6.6, 11.7 Hz), 1H total]; [3.17 (s) & 3.16 (s), 3H total]; [2.99 (m) & 2.93 (m), 1H total]; [2.83 (t, *J* = 4.1 Hz) & 2.82 (t, *J* = 4.5 Hz), 1H total]; 2.70-2.60 (m, 1H); 2.45-2.30 (m, 1H).

Example 43

Diol 162: The epoxide 161 (437 mg, 1.23 mmol) was gently relaxed for 1 h in THF (20 mL) and H₂O (10 mL) containing 5 drops of 70% HClO₄. Solid
30 NaHCO₃ was added and the mixture concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with brine and dried. Concentration *in vacuo* gave the crude diol 162 as a pale oil in quantitative yield. Used without any purification for the next reaction.

Example 44

Aldehyde 163: Oxidation of diol 162 was carried out according to the procedure of Vo-Quang and co-workers, "Synthesis", 68 (1988). To a slurry of silica gel (4.3 g) in dichloromethane (30 mL) was added a solution of NaIO₄ (4.4 mL of a 0.65 M aqueous solution). To this slurry was added a solution of the crude diol 162 (520 mg) in EtOAc (5 mL) and dichloromethane (15 mL). After 1 h the solids were filtered and washed with 20% hexanes/EtOAc. Concentration gave an oily residue which was dissolved in EtOAc and dried over MgSO₄. Concentration *in vacuo* gave the aldehyde 163 as a pale oil which was used immediately for the next reaction. ¹H NMR (CDCl₃, 300 MHz): δ 9.69 (s, 1H); 6.98 (m, 1H); 4.72 (dd, 1H, *J* = 3.7, 9.1 Hz); 4.53 (d, 1H, *J* = 18.3 Hz); 4.45 (d, 1H, *J* = 18.3 Hz); 4.31 (m, 1H); 4.26-4.18 (m, 1H); 3.79 (s, 3H); 3.19 (s, 3H); 3.05 (dd, 1H, *J* = 5.7, 18.6 Hz); 2.20-2.45 (m, 1H).

Example 45

Alcohol 164: The crude aldehyde 163 was treated with NaCNBH₃ according to the procedure of Borch and co-workers, "J. Amer. Chem. Soc.", 93:2897 (1971) to give 269 mg (65%) of the alcohol 164 after flash chromatography (40% hexanes in ethyl acetate). ¹H NMR (CDCl₃, 300 MHz): δ 6.91 (m, 1H); 4.75 (dd, 1H, *J* = 3.9, 8.7 Hz); 4.34 (br t, 1H, *J* = 4.1 Hz); 4.25-4.15 (m, 1H); 3.85-3.70 (m, 4H); 3.77 (s, 3H); 3.16 (s, 3H); 2.95 (dd, 1H, *J* = 5.7, 18.6 Hz); 2.37 (dd, 1H, *J* = 7.1, 18.6 Hz); 2.26 (br s, 1H).

Example 46

Aziridine 165: The alcohol 164 (208 mg, 0.62 mmol) was acetylated in the usual manner (AcCl, pyridine, dichloromethane, cat. DMAP) to give the acetate (241 mg, 100%). The crude acetate (202 mg, 0.54 mmol) was treated at room temperature with Ph₃P (155 mg) in THF (12 mL) for 2 h. H₂O (1.1 mL) and triethylamine (224 μL) were then added and the solution stirred overnight. The reaction mixture was concentrated and the residue partitioned between ethyl acetate and saturated bicarbonate/brine. The organic layer was dried, concentrated *in vacuo* and purified by flash chromatography (10% MeOH in EtOAc) to give 125 mg (90%) of aziridine 165 as a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 6.80 (m, 1H); 4.44 (br s, 1H); 4.23 (t, 2H, *J* = 4.8 Hz); 3.82-3.65 (m, 2H); 3.74 (s, 3H); 2.85 (br d, 1H, *J* = 19.2 Hz); 2.65-2.40 (m, 3H); 2.09 (s, 3H); 1.25 (br s, 1H).

Example 47

N-Boc aziridine 166: Boc anhydride (113 mg, 0.52 mmol) was added to a solution of aziridine 165 (125 mg, 0.49 mmol), triethylamine (70 μ L), DMAP (cat. amount) in dichloromethane (7 mL). After 1 h the reaction was concentrated and the residue subjected to flash chromatography (40% EtOAc in hexanes) to give 154 mg (88%) of the N Boc aziridine 166 as a pale oil. ^1H NMR (CDCl_3 , 300 MHz): δ 6.82 (m, 1H); 4.47 (br m, 1H); 4.23 (t, 2H, $J = 4.7$ Hz); 3.81 (t, 2H, $J = 4.7$ Hz); 3.75 (s, 3H); 3.00 (br d, 1H, $J = 18.0$ Hz); 2.90-2.85 (m, 2H); 2.65-2.55 (m, 1H); 2.10 (s, 3H); 1.44 (s, 9H).

Example 48

Azido ester 167: Aziridine 166 (154 mg, 0.43 mmol), sodium azide (216 mg), and ammonium chloride (223 mg) was heated at 100°C in DMF (5 mL) for 18 h. The cooled reaction mixture was partitioned between ethyl ether and brine. The ether layer was washed with H_2O , brine and dried over MgSO_4 . Concentration gave a crude residue which was treated with 40% TFA in dichloromethane at room temperature. After 2 h the reaction was concentrated *in vacuo* to give a pale oil which was passed through a short column of silica gel eluting with EtOAc. The product was then acylated in the usual manner (AcCl , pyridine, dichloromethane, cat. DMAP) to give the azido ester 167 as a pale yellow oil 16 mg (11% for 3 steps) after flash chromatography (5% MeOH in chloroform). ^1H NMR (CDCl_3 , 300 MHz): δ 6.85 (m, 1H); 5.80 (br d, 1H, $J = 7.8$ Hz); 4.55 (m, 1H); 4.25-4.10 (m, 3H); 3.90-3.85 (m, 2H); 3.78 (s, 3H); 3.55 (m, 1H); 2.90 (dd, 1H, $J = 5.4, 17.0$ Hz); 2.45-2.25 (m, 1H); 2.10 (s, 3H); 2.05 (s, 3H).

Example 49

Amino acid 168: To a solution of ester 167 (16 mg, 0.047 mmol) in THF (1 mL) cooled to 0 °C was added aq. KOH (208 μ L of a 0.476 M solution). The reaction was then warmed to room temperature and stirred for 2 h. The reaction was then acidified to pH = 4.0 with Amberlite IR-120 (plus) acidic resin. The resin was then filtered and washed with ethanol and H_2O . Concentration *in vacuo* gave a 14 mg (100%) of the azido carboxylic acid as a white solid. The azido acid was dissolved in ethanol (2 mL) and treated with hydrogen gas (1 atm) over Lindlar's catalyst (15 mg) for 16 h according to the procedure of Corey and co-workers, "Synthesis", 590 (1975). The reaction

mixture was filtered through a celite pad and washed with hot ethanol and H₂O. Concentration *in vacuo* gave a pale orange solid which was purified by a C₁₈ column chromatography eluting with H₂O. The fractions containing the product were pooled and lyophilized to give 9.8 mg of 168 as a white powder. ¹H NMR (D₂O, 500 MHz): δ: 6.53 (br s, 1H); 4.28 (br m, 1H); 4.08 (dd, 1H, *J* = 11.0, 11.0 Hz); 3.80-3.65 (complex m, 4H); 3.44 (m, 1H); 2.84 (apparent dd, 1H); 2.46-2.39 (complex m, 1H); 2.08 (s, 3H).

Example 50

Epoxy MOM ether 19 (PG=methoxymethyl): Prepared in 74% from epoxy alcohol 1 according to the procedure of Mordini and co-workers, "J. Org. Chem.", 59:4784 (1994). ¹H NMR (CDCl₃, 300 MHz): δ 6.73 (m, 1H); 4.87 (s, 2H); 4.59 (t, 1H, *J* = 2.4 Hz); 3.76 (s, 3H); 3.57 (m, 1H); 3.50-3.40 (m, 1H); 3.48 (s, 3H); 3.10(d, *J* = 19.5 Hz); 2.45 (m, 1H).

Example 51

Aziridine 170: Prepared in 77% overall from epoxide 19 (PG=methoxymethyl) according to the general protocol described in Examples 3 and 4: ¹H NMR (CDCl₃, 300 MHz): δ 6.85 (m, 1H); 4.78 (s, 2H); 4.54 (m, 1H); 3.73 (s, 3H); 3.41 (s, 3H); 2.87 (d, 1H, *J* = 18.9 Hz); 2.70-2.45 (m, 3H).

Example 52

Azido ester 22 (PG=methoxymethyl): The aziridine 170 (329 mg, 1.54 mmol), NaN₃ (446 mg) and NH₄Cl (151 mg) was heated at 65°C in DMF (20 mL) for 18 h. The cooled reaction mixture was partitioned between ethyl ether and brine. The ether layer was washed with H₂O, brine and dried over MgSO₄. Concentration *in vacuo* gave the crude azido amine as a pale oil which was taken up in CH₂Cl₂ (15 mL) and treated with pyridine (4 mL) and AcCl (150 μL). Aqueous work up followed by flash chromatography of the residue gave 350 mg (76%) of azido ester 22 (PG=methoxymethyl) as a pale oil. ¹H NMR (CDCl₃, 300 MHz): δ 6.78 (s, 1H); 6.39 (br d, 1H, *J* = 7.8 Hz); 4.72 (d, 1H, *J* = 6.9 Hz); 4.66 (d, 1H, *J* = 6.9 Hz); 4.53 (br d, 1H, *J* = 8.4 Hz); 4.00-3.90 (m, 1H); 3.80-3.65 (m, 1H); 3.75 (s, 3H); 3.37 (s, 3H); 2.85 (dd, 1H, *J* = 5.4, 17.7 Hz); 2.35-2.20 (m, 1H); 2.04 (s, 3H).

Example 53

Amino acid 114: The azide 22 (PG=methoxymethyl) (39 mg, 0.131 mmol) was treated with hydrogen gas at 1 atmosphere over Lindlar's catalyst (39 mg) in ethanol for 2.5 h according to the procedure of Corey and co-

workers, "Synthesis", 590 (1975). The reaction mixture was filtered through a celite pad, washed with hot ethanol and concentrated to give the crude amine 33 mg (92%) as a pale foam. The amine in THF (1 mL) was treated with aq. KOH (380 μ L of a 0.476 M solution). After 1 h the reaction was acidified to pH = 4.0 with Amberlite IR-120 (plus) acidic resin. The resin was then filtered, washed with H₂O and concentrated to give a pale solid which was purified by a C₁₈ column chromatography eluting with H₂O. The fractions containing the product were pooled and lyophilized to give 20 mg of 114 as a white powder. ¹H NMR (D₂O, 300 MHz): δ 6.65 (s, 1H); 4.87 (d, 1H, *J* = 7.5 Hz); 4.76 (d, 1H, *J* = 7.5 Hz); 4.47 (br d, 1H, *J* = 8.7 Hz); 4.16 (dd, 1H, *J* = 11.4, 11.4 Hz); 3.70-3.55 (m, 1H); 3.43 (s, 3H); 2.95 (dd, 1H, *J* = 5.7, 17.4 Hz); 2.60-2.45 (m, 1H); 2.11 (s, 3H).

Example 54

Amino acid 171: To solid amino acid 114 (4 mg, 0.015 mmol) was added 40% TFA in CH₂Cl₂ (1 mL, cooled to 0°C prior to addition). After stirring at room temperature for 1.5 h the reaction mixture was concentrated to give a white foam. Co-evaporation from H₂O several times followed by lyophilization gave a white solid, 5.5 mg of 117 as the TFA salt. ¹H NMR (D₂O, 300 MHz): δ 6.85 (m, 1H); 4.45 (m, 1H); 4.05 (dd, 1H, *J* = 11.4, 11.4 Hz); 3.65-3.55 (m, 1H); 3.00-2.90 (m, 1H); 2.60-2.45 (m, 1H); 2.09 (s, 3H).

Example 55

Acetonide 180: To a suspension of shikimic acid (25 g, 144 mmol, Aldrich) in methanol (300 mL) was added *p*-toluenesulfonic acid (274 mg, 1.44 mmol, 1 mol%) and the mixture was heated to reflux for 2h. After adding more *p*-toluenesulfonic acid (1 mol%) the reaction was refluxed for 26h and was evaporated. The crude methyl ester (28.17 g) was suspended in acetone (300 mL) and was treated with dimethoxypropane (35 mL, 288 mmol) and was stirred at room temperature for 6h and then was evaporated. The crude product was dissolved in ethyl acetate (400 mL) and was washed with saturated NaHCO₃ (3X125 mL) and saturated NaCl. The organic phase was dried (MgSO₄), filtered, and evaporated to afford crude acetonide 180 (~29.4 g) which was used directly: ¹H NMR (CDCl₃) δ 6.91 (t, 1H, *J* = 1.1), 4.74 (t, 1H, *J* = 4.8), 4.11 (t, 1H, *J* = 6.9), 3.90 (m, 1H), 2.79 (dd, 1H, *J* = 4.5, 17.4), 2.25 (m, 2H), 1.44 (s, 3H), 1.40 (s, 3H).

Example 56

Mesylate 130: To a solution of acetone 180 (29.4 g, 141 mmol) in CH_2Cl_2 (250 mL) at 0°C was added triethylamine (29.5 mL, 212 mmol) followed by the addition of methanesulfonyl chloride (13.6 mL, 176 mmol) over a period of 10 min. The reaction was stirred at 0°C for 1 h and ice cold water (250 mL) was added. After transfer to a separatory funnel, the organic phase was washed with water, 5% citric acid (300 mL), saturated NaHCO_3 (300 mL) and was dried (MgSO_4), filtered, and evaporated. The crude product was filtered through a short plug of silica gel on a fritted glass funnel eluting with ethyl acetate. The filtrate was evaporated to afford mesylate 130 (39.5 g, 91%) as a viscous oil which was used directly in the next step: ^1H NMR (CDCl_3) δ 6.96 (m, 1H), 4.80 (m, 2H), 4.28 (dd, 1H, $J = 6.6, 7.5$), 3.79 (s, 3H), 3.12 (s, 3H), 3.01 (dd, 1H, $J = 5, 17.7$), 2.56-2.46 (m, 1H).

Example 57

Diol 131: To a solution of mesylate 130 (35.85 g, 117 mmol) in methanol (500 mL) was added *p*-toluenesulfonic acid (1.11 g, 5.85 mmol, 5 mol%) and the solution was refluxed for 1.5 h and was evaporated. The residue was redissolved in methanol (500 mL) and was refluxed an additional 4 h. The solvent was evaporated and the crude oil was triturated with diethyl ether (250 mL). After completing the crystallization overnight at 0°C , the solid was filtered and was washed with cold diethyl ether, and dried to afford diol 131 (24.76 g) as a white solid. Evaporation of the filtrate and crystallization of the residue from methanol/diethyl ether gave an additional 1.55 g. Obtained 26.3 g (85%) of diol 131: ^1H NMR (CD_3OD) δ 6.83 (m, 1H), 4.86 (m, 1H), 4.37 (t, 1H, $J = 4.2$), 3.87 (dd, 1H, $J = 4.2, 8.4$), 3.75 (s, 3H), 3.13 (s, 3H), 2.98-2.90 (m, 1H), 2.53-2.43 (m, 1H).

Example 58

Epoxy alcohol 1: A suspension of diol 131 (20.78g, 78 mmol) in tetrahydrofuran (400 mL) at 0°C was treated with 1, 8-diazabicyclo[5.4.0]undec-7-ene (11.7 mL, 78 mmol) and was stirred at room temperature for 9 h at which time the reaction was complete. The reaction was evaporated and the crude residue was dissolved in CH_2Cl_2 (200 mL) and was washed with saturated NaCl (300 mL). The aqueous phase was extracted with CH_2Cl_2 (2X200 mL). The combined organic extracts were dried (MgSO_4), filtered, and

evaporated. The crude product was purified on silica gel (ethyl acetate) to afford epoxy alcohol 1 (12 g, 90%) as a white solid whose ^1H NMR spectrum was consistent with that reported in the literature: McGowan, D. A.; Berchtold, G. A., "J. Org. Chem.", 46:2381 (1981).

5 Example 59

Methoxymethyl ether 22 (PG=methoxymethyl): To a solution of epoxy alcohol 1 (4 g, 23.5 mmol) in CH_2Cl_2 (100 mL) was added N, N'-diisopropylethylamine (12.3 mL, 70.5 mmol) followed by chloromethyl methyl ether (3.6 mL, 47 mmol, distilled from tech. grade). The solution was
10 refluxed for 3.5 h and the solvent was evaporated. The residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The aqueous phase was extracted with ethyl acetate (100 mL). The combined organic extracts were washed with saturated NaCl (100 mL), dried (MgSO_4), filtered, and evaporated to afford 4.9 g of a solid residue which was of suitable purity to
15 use directly in the next step: mp 62-65°(crude); mp 64-66°C (diethyl ether/hexane); ^1H NMR (CDCl_3) δ 6.73 (m, 1H), 4.87 (s, 2H), 4.59 (m, 1H), 3.75 (s, 3H), 3.57 (m, 1H), 3.48 (m overlapping s, 4H), 3.07 (dd, 1H, $J = 1.2, 19.8$), 2.47 (dq, 1H, $J = 2.7, 19.5$).

Ethyl Ester Analog of Compound 22:

20 To a solution of the corresponding ethyl ester of compound 1 (12.0g, 0.065 mol) in CH_2Cl_2 (277 mL) at room temperature was added diisopropylethyl amine (34.0 mL, 0.13 mol) followed by chloromethyl methyl ether (10.0 mL, 0.19 mol). The reaction mixture was then gently refluxed for 2 h, cooled, concentrated *in vacuo*, and partitioned between EtOAc and water.
25 The organic layer was separated and washed successively with dil. HCl, saturated bicarb, brine and dried over MgSO_4 . Concentration *in vacuo* followed by flash chromatography on silica gel (50% hexanes in EtOAc) gave 13.3 g (90%) of the corresponding ethyl ester of compound 22 as a colorless liquid. ^1H NMR(300 MHz, CDCl_3) δ 6.73-6.71 (m, 1H); 4.87 (s, 2H); 4.61-4.57
30 (m, 1H); 4.21 (q, 2H, $J = 7.2$ Hz); 3.60-3.55 (m, 1H); 3.50-3.45 (m, 1H); 3.48 (s, 3H); 3.12-3.05 (m, 1H); 2.52-2.42 (m, 1H); 1.29 (t, 3H, $J = 7.2$ Hz).

Example 60

Alcohol 181: To a solution of methoxymethyl ether 22 (PG=methoxymethyl) (4.9 g, 22.9 mmol) in 8/1-MeOH/ H_2O (175 mL, v/v) was
35 added sodium azide (7.44 g, 114.5 mmol) and ammonium chloride (2.69 g, 50.4 mmol) and the mixture was refluxed for 15 h. The reaction was diluted with

water (75 mL) to dissolve precipitated salts and the solution was concentrated to remove methanol. The resulting aqueous phase containing a precipitated oily residue was diluted to a volume of 200 mL with water and was extracted with ethyl acetate (3X100 mL). The combined organic extracts were washed
5 with saturated NaCl (100 mL), dried (MgSO₄), filtered and evaporated. The crude was purified on silica gel (1/1-hexane/ethyl acetate) to afford alcohol 181 (5.09 g, 86%) as a pale yellow oil. Subsequent preparations of alcohol 181 provided material which was of sufficient purity to use in the next step without further purification: ¹H NMR (CDCl₃) δ 6.86 (m, 1H), 4.79 (s, 2H),
10 4.31 (br t, 1H, J = 4.2), 3.90-3.75, 3.77 (m overlapping s, 5H), 3.43 (s, 3H), 2.92 (d, 1H, J = 6.6), 2.87 (dd, 1H, J = 5.4, 18.6), 2.21-2.30 (m, 1H).

Example 61

Mesylate 184: To a solution of alcohol 181 (6.47 g, 25.2 mmol) in CH₂Cl₂ (100 mL) at 0°C was added first triethyl amine (4.4 mL, 31.5 mmol) then
15 methanesulfonyl chloride (2.14 mL, 27.7 mmol). The reaction was stirred at 0°C for 45 min then was warmed to room temperature stirring for 15 min. The reaction was evaporated and the residue was partitioned between ethyl acetate (200 mL) and water (100 mL). The organic phase was washed with water (100 mL), saturated NaHCO₃ (100 mL), saturated NaCl (100 mL). The
20 water washes were extracted with a single portion of ethyl acetate which was washed with the same NaHCO₃/NaCl solutions. The combined organic extracts were dried (MgSO₄), filtered, and evaporated. The crude product was of suitable purity to be used directly in the next step: ¹H NMR (CDCl₃) δ 6.85 (m, 1H), 4.82 (d, 1H, J = 6.9), 4.73 (d, 1H, J = 6.9), 4.67 (dd, 1H, J = 3.9, 9.0), 4.53 (br
25 t, 1H, J = 4.2), 3.78 (s, 3H), 3.41 (s, 3H), 3.15 (s, 3H), 2.98 (dd, 1H, J = 6.0, 18.6), 2.37 (m, 1H); ¹³C NMR (CDCl₃) δ 165.6, 134.3, 129.6, 96.5, 78.4, 69.6, 55.8, 55.7, 52.1, 38.2, 29.1.

Example 62

Aziridine 170: To a solution of mesylate 184 (8.56 g, 25 mmol) in THF
30 (150 mL) at 0°C was added Ph₃P (8.2 g, 31 mmol), initially adding a third of the amount while cooling and then after removing the ice bath adding the remainder of the Ph₃P over a period of 10-15 min. After complete addition of the Ph₃P the reaction was stirred at room temperature for 3 h with the formation of a white precipitate. To this suspension was added triethyl amine
35 (5.2 mL, 37.5 mmol) and water (10 mL) and the mixture was stirred at room temperature for 12 h. The reaction was concentrated to remove THF and the

residue was partitioned between CH_2Cl_2 (200 mL) and saturated NaCl (200 mL). The aqueous phase was extracted with several portions of CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to afford a crude product which was purified on silica gel (10% MeOH/EtOAc) to afford aziridine 170 (4.18 g, 78%) as an oil which typically contained trace amounts of triphenylphosphine oxide impurity: ^1H NMR (CDCl_3) δ 6.81 (m, 1H), 4.78 (s, 2H), 4.54 (m, 1H), 3.73 (s, 3H), 3.41 (s, 3H), 2.87 (app dd, 1H), 2.64 (br s, 1H), 2.56-2.47 (m, 2H), NH signal was not apparent; ^{13}C NMR (CDCl_3) δ 166.9, 132.5, 128.0, 95.9, 69.5, 55.2, 51.6, 31.1, 27.7, 24.1.

Example 63

Amine 182: To a solution of aziridine 170 (3.2 g, 15 mmol) in DMF (30 mL) was applied a vacuum on a rotary evaporator (40°C) for several minutes to degas the solution. To the solution was added sodium azide (4.9 g, 75 mmol) and ammonium chloride (1.6 g, 30 mmol) and the mixture was heated at 65-70°C for 21 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (~100 mL) and was filtered. The filtrate was evaporated and the residue was partitioned between diethyl ether (100 mL) and saturated NaCl (100 mL). The organic phase was washed again with saturated NaCl (100 mL), dried (MgSO_4), filtered, and was evaporated. Additional crude product was obtained from the aqueous washings by extraction with ethyl acetate and treated in the same manner as described above. The crude product was purified on silica gel (5% MeOH/ CH_2Cl_2) to afford amine 182 (2.95 g) as an oil which contained a small amount of triphenylphosphine oxide impurity from the previous step: ^1H NMR (CDCl_3) δ 6.82 (t, 1H, $J = 2.3$), 4.81 (d, 1H, $J = 7.2$), 4.77 (d, 1H, $J = 6.9$), 4.09-4.04 (m, 1H), 3.76 (s, 3H), 3.47 and 3.44 (m overlapping s, 4H), 2.94-2.86 (m, 2H), 2.36-2.24 (m, 1H); ^{13}C NMR (CDCl_3) δ 165.9, 137.3, 128.2, 96.5, 79.3, 61.5, 55.7, 55.6, 51.9, 29.5.

Example 64

N-Triethyl aziridine 183: Amine 182 (2.59 g, 10.2 mmol) was dissolved in 5% HCl/MeOH (30 mL) and the solution was stirred for 3 h at room temperature. Additional 5% HCl/MeOH (10 mL) was added stirring 1 h and the solvent was evaporated to afford 2.52 g of the HCl salt as a tan solid after high vacuum. To a suspension of the HCl salt in CH_2Cl_2 (50 mL) at 0°C was added triethylamine (3.55 mL, 25.5 mmol) followed by the addition of solid

trityl chloride (5.55 g, 12.8 mmol) in one portion. The mixture was stirred at 0°C for 1 h and then was warmed to room temperature stirring for 2 h. The reaction was cooled to 0°C, triethylamine (3.6 mL, 25.5 mmol) was added and methane sulfonyl chloride (0.97 mL, 12.5 mmol) was added, stirring the
5 resulting mixture for 1 h at 0°C and for 22 h at room temperature. The reaction was evaporated and the residue was partitioned between diethyl ether (200 mL) and water (200 mL). The organic phase was washed with water (200 mL) and the combined aqueous phases were extracted with diethyl ether (200 mL). The combined organic extracts were washed with water (100 mL),
10 saturated NaCl (200 mL) and were dried (Na₂SO₄), filtered, and evaporated. The crude product was purified on silica gel (1/1-hexane/CH₂Cl₂) to afford N-trityl aziridine 183 (3.84 g, 86%) as a white foam: ¹H NMR (CDCl₃) δ 7.4-7.23 (m, 16H), 4.32 (m, 1H), 3.81 (s, 3H), 3.06 (dt, 1H, J = 1.8, 17.1), 2.94-2.86 (m, 1H), 2.12 (m, 1H), 1.85 (t, 1H, J = 5.0).

15 Example 65

Compound 190: A solution of N-trityl aziridine 183 (100 mg, 0.23 mmol), cyclohexanol (2 mL) and boron trifluoride etherate (42 µL, 0.35 mmol) was heated at 70°C for 1.25 h and was evaporated. The residue was dissolved in pyridine (2 mL) and was treated with acetic anhydride (110 µL, 1.15 mmol)
20 and catalytic DMAP. After stirring for 3 h at room temperature the reaction was evaporated. The residue was partitioned between ethyl acetate and 5% citric acid. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with saturated NaHCO₃, and saturated NaCl. The organic phase was dried (MgSO₄), filtered, and
25 evaporated. The crude product was purified on silica gel (1/1-hexane/ethyl acetate) to afford compound 190 (53 mg, 69%) as a solid: mp 105-107°C (ethyl acetate/hexane); ¹H NMR (CDCl₃) δ 6.78 (m, 1H), 6.11 (d, 1H, J = 7.4), 4.61 (m, 1H), 4.32-4.23 (m, 1H), 3.76 (s, 3H), 3.44-3.28 (m, 2H), 2.85 (dd, 1H, J = 5.7, 17.6), 2.28-2.17 (m, 1H), 2.04 (s, 3H), 1.88-1.19 (m, 10H).

30 Example 66

Compound 191: To a solution of compound 190 (49 mg, 0.15 mmol) in THF was added triphenylphosphine (57 mg, 0.22 mmol) and water (270 µL) and the solution was heated at 50°C for 10 h. The reaction was evaporated and the residue was dissolved in ethyl acetate, dried (Na₂SO₄), filtered and
35 evaporated. The crude product was purified on silica gel (1/1-methanol/ethyl acetate) to afford the amine (46 mg) as a pale yellow solid. The a solution of

the amine in THF (1.5 mL) was added 1.039N KOH solution (217 μ L) and water (200 μ L). The mixture was stirred at room temperature for 1 h and was then cooled to 0°C and acidified to pH 6-6.5 with IR 120 ion exchange resin. The resin was filtered, washed with methanol and the filtrate was evaporated.

5 The solid residue was dissolved in water and was passed through a column (4X1 cm) of C-18 reverse phase silica gel eluting with water and then 2.5% acetonitrile/water. Product fractions were combined and evaporated and the residue was dissolved in water and lyophilized to afford amino acid 191 (28 mg) as a white solid: ^1H NMR (D_2O) δ 6.47 (br s, 1H), 4.80 (br d, 1H), 4.00 (dd, 1H, $J = 8.9, 11.6$), 3.59-3.50 (m, 2H), 2.87 (dd, 1H, $J = 5.5, 17.2$), 2.06 (s, 3H), 1.90-1.15 (series of m, 10H); Anal. Calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$: C, 57.31; H, 8.34; N, 8.91. Found: C, 57.38; H, 8.09; N, 8.77.

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Example 67

bis-Boc guanidino ester 201: Treated according to the procedure of Kim and Qian, "Tetrahedron Lett.", 34:7677 (1993). To a solution of amine 200 (529 mg, 1.97 mmol, prepared by the method of Example 109, bis-Boc thiourea (561 mg, 2.02 mmol) and Et_3N (930 μ L) in dry DMF (5.0 mL) cooled to 0°C was added HgCl_2 (593 mg, 2.18 mmol) in one portion. The heterogeneous reaction mixture was stirred for 45 min at 0°C and then at room temperature for 15 min, after which the reaction was diluted with EtOAc and filtered through a pad of celite. Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (10% hexanes in ethyl acetate) gave 904 mg (90%) of 201 as a pale oil. ^1H NMR (CDCl_3 , 300 MHz): δ 11.39 (s, 1H); 8.63 (d, 1H, $J = 7.8$ Hz); 6.89 (t, 1H, $J = 2.4$ Hz); 6.46 (d, 1H, $J = 8.7$ Hz); 4.43-4.32 (m, 1H); 4.27-4.17 (m, 1H); 4.13-4.06 (m, 1H); 3.77 (s, 3H); 3.67-3.59 (m, 1H); 2.83 (dd, 1H, $J = 5.1, 17.7$ Hz); 2.45-2.33 (m, 1H); 1.95 (s, 3H); 1.65-1.50 (m, 2H); 1.45 (s, 18H); 0.90 (t, 3H, $J = 7.5$ Hz).

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Example 68

Carboxylic acid 202: To a solution of methyl ester 201 (904 mg, 1.77 mmol) in THF (10 mL) was added aqueous KOH (3.45 mL of a 1.039 N solution). The reaction mixture was stirred at room temperature for 17 h, cooled to 0°C and acidified to pH 4.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the free acid as a pale foam which was used without further purification in the next reaction.

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Example 69

Guanidine carboxylic acid 203: To a solution of bis-Boc guanidnyl acid 202 (crude from previous reaction) in CH₂Cl₂ (40 mL) cooled to 0°C was added neat trifluoroacetic acid (25 mL). The reaction mixture was stirred at 0°C for 1 h and then at room temperature for 2 h. Concentration *in vacuo* gave a pale orange solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 495 mg (68%, 2 steps) of the guanidine carboxylic acid 203 as the trifluoroacetic acid salt. ¹H NMR (D₂O, 300 MHz): δ 6.66 (s, 1H); 4.29 (bd, 1H, *J* = 9.0 Hz); 4.01 (dd, 1H, *J* = 10.8, 10.8 Hz); 3.87-3.79 (m, 1H); 3.76-3.67 (m, 1H); 3.60-3.50 (m, 1H); 2.83 (dd, 1H, *J* = 5.1, 17.4 Hz); 2.47-2.36 (m, 1H); 2.06 (s, 3H); 1.65-1.50 (m, 2H); 0.90 (t, 3H, *J* = 7.2 Hz). Anal. Calcd for C₁₅H₂₃O₆N₄F₃: C, 43.69; H, 5.62; N, 13.59. Found: C, 43.29; H, 5.90; N, 13.78.

Example 70

Formamidine carboxylic acid 204: A solution of amino acid 102 (25 mg, 0.10 mmol, prepared by the method of Example 110) in water (500 µL) at 0 - 5°C was adjusted to pH 8.5 with 1.0 N NaOH. Benzyl formimidate hydrochloride (45 mg, 0.26 mmol) was added in one portion and the reaction mixture was stirred for 3 h at this temperature while maintaining the pH at 8.5 - 9.0 with 1.0 N NaOH. The reaction was then concentrated *in vacuo* and purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 4.0 mg (13%) of the formamidine carboxylic acid 204. ¹H NMR (D₂O, 300 MHz): δ 7.85 (s, 1H); 6.53 (bd, 1H, *J* = 7.8 Hz); 4.32-4.25 (bm, 1H); 4.10-3.97 (m, 1H); 3.76-3.67 (m, 2H); 3.57-3.49 (m, 1H); 2.86-2.81 (m, 1H); 2.55-2.40 (m, 1H); 2.04 (s, 3H); 1.65-1.50 (m, 2H); 0.90 (t, 3H, *J* = 7.4 Hz).

Example 71

Amino acid 206: To a solution of amino methyl ester 205 (84 mg, 0.331 mmol, prepared by Example 107) in THF (1.0 mL) was added aqueous KOH (481 µL of a 1.039 N solution). The reaction mixture was stirred at room temperature for 2.5 h and acidified to pH 6.5 with Amberlite IR-120 (H⁺) acidic resin. The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the amino acid as a white solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 59 mg (74%) of the amino acid 206. ¹H NMR (CD₃OD, 300 MHz): δ 6.60 (bd, 1H, *J* = 1.8

Hz); 4.01-3.95 (m, 1H); 3.71-3.60 (m, 2H); 3.50-3.42 (m, 1H); 3.05-2.85 (m, 2H); 2.39-2.28 (m, 1H); 1.70-1.55 (m, 2H); 0.95 (t, 3H, $J = 7.5$ Hz).

Example 72

Trifluoroacetamide 207: To a degassed solution of amino acid 206 (59 mg, 0.246 mmol) in dry methanol (1.0 mL) under argon was added Et₃N (35 μ L) followed by methyl trifluoroacetate (35 μ L). The reaction was stirred for one week at room temperature and concentrated. Analysis by ¹H NMR showed that reaction was 40% complete. The crude reaction product was redissolved in dry methanol (1.0 mL), methyl trifluoroacetate (1.0 mL) and Et₃N (0.5 mL) and stirred at room temperature for 5 days. The reaction was then concentrated *in vacuo* and dissolved in 50% aqueous THF (2.0 mL), acidified to pH 4 with Amberlite IR-120 (H⁺) acidic resin and filtered. Concentration gave the crude trifluoroacetamide carboxylic acid which was used without further purification for the next reaction.

Example 73

Amino acid 208: A solution of azide 207 (crude from previous reaction) in THF (2.0 mL) and water (160 μ L) was treated with polymer supported triphenyl phosphine (225 mg) at room temperature. After stirring for 20 h the polymer was filtered and washed with methanol. Concentration *in vacuo* gave a pale solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 6.5 mg (9 %) of the trifluoroacetamide amino acid 208. ¹H NMR (D₂O, 300 MHz): δ 6.59 (bs, 1H); 4.40-4.30 (m, 1H); 4.26 (t, 1H, $J = 10.1$ Hz); 3.80-3.66 (m, 2H); 3.56-3.47 (m, 1H); 2.96 (bdd, 1H, $J = 5.4, 17.7$ Hz); 2.58-2.45 (m, 1H); 1.62 - 1.50 (m, 2H); 0.89 (t, 3H, $J = 7.5$ Hz).

Example 74

Methylsulfonamide methyl ester 209: Methanesulfonyl chloride (19 μ L) was added to a solution of amine 205 (58 mg, 0.23 mmol, prepared by Example 107), Et₃N (97 μ L) and a catalytic amount of DMAP (few crystals) in CH₂Cl₂ (1.0 mL) at 0°C. After 30 min the reaction mixture was warmed to room temperature and stirred for an additional 1 h. Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (50% hexanes in ethyl acetate) gave 61 mg (79%) of the sulfonamide 209. ¹H NMR (CDCl₃, 300 MHz): δ 6.87 (t, 1H, $J = 2.3$ Hz); 5.08 (d, 1H, $J = 7.5$ Hz); 4.03-3.90 (m, 1H); 3.78 (s,

3H); 3.75-3.45 (m, 4H); 3.14 (s, 3H); 2.95 (dd, 1H, $J = 5.2, 17.3$ Hz); 2.42-2.30 (m, 1H); 1.75-1.55 (m, 2H); 0.95 (t, 3H, $J = 7.5$ Hz).

Example 75

Amino ester 210: A solution of azide 209 (61 mg, 0.183 mmol) in THF (2.0 mL) and water (118 μ L) was treated with polymer supported triphenyl phosphine (170 mg) at room temperature. After stirring for 17.5 h the polymer was filtered and washed with methanol. Concentration *in vacuo* followed by flash chromatography of the residue through a short silica gel column (100% methanol) gave 45 mg (80%) of the amino ester 210 as a pale foam. ^1H NMR (CDCl_3 , 300 MHz): δ 6.85 (s, 1H); 3.94 (bd, 1H, $J = 7.8$ Hz); 3.77 (s, 3H); 3.74-3.60 (m, 2H); 3.55-3.45 (m, 1H); 3.25-3.15 (m, 1H); 3.11 (s, 3H); 2.94-2.85 (m, 1H); 2.85 (bs, 2H); 2.22-2.10 (m, 1H); 1.70-1.56 (m, 2H); 0.94 (t, 3H, $J = 7.5$ Hz).

Example 76

Amino acid 211: A solution of methyl ester 210 (21 mg, 0.069 mmol) in THF (200 μ L) was treated with aqueous KOH (135 μ L of a 1.039 N solution). The reaction mixture was stirred at room temperature for 40 min and neutralized to pH 7.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the amino acid as a pale solid which was purified by C_{18} reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 3.5 mg (17%) of the amino acid 211. ^1H NMR (D_2O , 300 MHz): δ 6.60 (d, 1H, $J = 1.8$ Hz); 4.30-4.20 (m, 1H); 3.84-3.75 (m, 1H); 3.68-3.58 (m, 1H); 3.60-3.40 (m, 2H); 3.20 (s, 3H); 2.96-2.88 (m, 1H); 2.55-2.45 (m, 1H); 1.72-1.59 (m, 2H); 0.93 (t, 3H, $J = 7.4$ Hz).

Example 77

Bis-Boc guanidino ester 212: Treated according to the procedure of Kim and Qian, "Tetrahedron Lett." 34:7677 (1993). To a solution of amine 210 (31 mg, 0.101 mmol), bis-Boc thiourea (28.5 mg, 0.103 mmol) and Et_3N (47 μ L) in dry DMF (203 μ L) cooled to 0°C was added HgCl_2 (30 mg, 0.11 mmol) in one portion. The heterogeneous reaction mixture was stirred for 30 min at 0°C and then at room temperature for 30 min, after which the reaction was diluted with EtOAc and filtered through a pad of celite. Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (40% hexanes in ethyl acetate) gave 49 mg (89%) of 212 as a pale oil. ^1H NMR

(CDCl₃, 300 MHz): δ 11.47 (s, 1H); 8.66 (d, 1H, J = 8.4 Hz); 6.87 (s, 1H); 6.01 (bs, 1H); 4.50-4.35 (m, 1H); 4.04 (bd, 1H, J = 8.4 Hz); 3.76 (s, 3H); 3.70-3.60 (m, 1H); 3.53-3.45 (m, 2H); 3.02 (s, 3H); 2.85 (dd, 1H, J = 5.3, 17.3 Hz); 2.42-2.30 (m, 1H); 1.66-1.55 (m, 2H); 1.49 (s, 9H); 1.48 (s, 9H); 0.93 (t, 3H, J = 7.3 Hz).

5 Example 78

Carboxylic acid 213: To a solution of methyl ester 212 (49 mg, 0.090 mmol) in THF (1.0 mL) was added aqueous KOH (260 μ L of a 1.039 N solution). The reaction mixture was stirred at room temperature for 16 h, cooled to 0°C and acidified to pH 4.0 with Amberlite IR-120 (H⁺) acidic resin.
10 The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the free acid as a pale foam which was used without further purification in the next reaction.

Example 79

Guanidine carboxylic acid 214: To a solution of bis-Boc guanidnyl acid
15 213 (crude from previous reaction) in CH₂Cl₂ (2.0 mL) cooled to 0°C was added neat trifluoroacetic acid (2.0 mL). The reaction mixture was stirred at 0°C for 1 h and then at room temperature for 1 h. Concentration *in vacuo* gave a pale orange solid which was purified by C₁₈ reverse phase
20 chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 10 mg (25%, 2 steps) of the guanidine carboxylic acid 214. ¹H NMR (D₂O, 300 MHz): δ 6.60 (bs, 1H); 4.22 (bd, 1H, J = 9.0 Hz); 3.82-3.66 (m, 2H); 3.65-3.54 (m, 1H); 3.43 (bt, 1H, J = 9.9 Hz); 3.15 (s, 3H); 2.82 (dd, 1H, J = 5.0, 17.5 Hz); 2.48-2.30 (m, 1H); 1.71-1.58 (m, 2H); 0.93 (t, 3H, J = 7.3 Hz).

25 Example 80

Propionamide methyl ester 215: Propionyl chloride (96 μ L, 1.1 mmol) was added to a solution of amine 205 (178 mg, 0.70 mmol, prepared by Example 107) and pyridine (1.5 mL) in CH₂Cl₂ (2.0 mL) cooled to 0°C. After 30 min at 0°C the reaction was concentrated and partitioned between ethyl
30 acetate and brine. The organic layer was separated and washed sequentially with saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (40% hexanes in ethyl acetate) gave 186 mg (86%) of the propionamide methyl ester 215 as a pale yellow solid. ¹H NMR (CDCl₃, 300
35 MHz): δ 6.86 (t, 1H, J = 2.3 Hz); 5.72 (bd, 1H, J = 7.8 Hz); 4.52-4.49 (m, 1H); 4.25-

4.15 (m, 1H); 3.77 (s, 3H); 3.65-3.37 (complex m, 3H); 2.87 (dd, 1H, $J = 5.7, 17.7$ Hz); 2.28 (q, 2H, $J = 7.5$ Hz); 2.25-2.20 (m, 1H); 1.65-1.50 (m, 2H); 1.19 (t, 3H, $J = 7.5$ Hz); 0.92 (t, 3H, $J = 7.5$ Hz).

Example 81

5 **Amino methyl ester 216:** A solution of azide 215 (186 mg, 0.60 mmol) in THF (5.0 mL) and water (400 μ L) was treated with polymer supported triphenyl phosphine (560 mg) at room temperature. After stirring for 21 h the polymer was filtered and washed with methanol. Concentration *in vacuo* gave the crude amino ester 216 which was used without any further
10 purification for the next step.

Example 82

15 **Amino acid 217:** A solution of methyl ester 216 (crude from previous reaction) in THF (500 μ L) was treated with aqueous KOH (866 μ L of a 1.039 N solution). The reaction mixture was stirred at room temperature for 3 h and
20 neutralized to pH 7.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the amino acid as a pale solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 49 mg (31% 2 steps) of the amino acid 217.
20 ¹H NMR (D₂O, 300 MHz): δ 6.54 (s, 1H); 4.25 (bd, 1H, $J = 8.7$ Hz); 4.13 (dd, 1H, $J = 9.0, 11.3$ Hz); 3.74-3.60 (m, 1H); 3.61-3.40 (m, 2H); 2.85 (dd, 1H, $J = 5.9, 17.1$ Hz); 2.55-2.40 (m, 1H); 2.35 (q, 2H, $J = 7.5$ Hz); 1.65-1.45 (m, 2H); 1.13 (t, 3H, $J = 7.5$ Hz); 0.88 (t, 3H, $J = 7.5$ Hz).

Example 83

25 **(mono methyl) bis-Boc guanidino ester 218:** To a solution of amine 200 (51 mg, 0.19 mmol) and mono methyl bis-Boc thiourea (36 mg, 0.19 mmol) in dry DMF (1.0 mL), was added 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (38 mg) and Et₃N (56 μ L) at room temperature. After 1.5 h at room temperature HgCl₂ (~75 mg, excess) was
30 added in one portion. The heterogeneous reaction mixture was stirred for 45 min, diluted with ethyl acetate and filtered through a pad of celite. The filtrate was diluted with additional ethyl acetate and washed with dilute HCl, saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (10%
35 methanol in ethyl acetate) gave 13 mg (16%) of the (mono methyl) bis-Boc

guanidino ester **218** as a colorless foam. ^1H NMR (CDCl_3 , 300 MHz): δ 6.84 (s, 1H); 6.20 (bd, 1H, $J = 5.1$ Hz); 5.45 (bs, 1H); 4.25-4.40 (bm, 1H); 4.20-4.05 (bm, 2H); 3.76 (s, 3H); 3.60-3.50 (m, 1H); 3.43-3.30 (m, 1H); 2.90 (dd, 1H, $J = 5.4, 17.7$ Hz); 2.77 (d, 3H, $J = 4.8$ Hz); 2.35-2.25 (m, 1H); 1.96 (s, 3H); 1.60-1.50 (m, 2H); 1.47 (s, 9H); 0.91 (t, 3H, $J = 7.2$ Hz).

Example 84

(mono methyl) bis-Boc guanidino acid **219**: To a solution of methyl ester **218** (13 mg, 0.031 mmol) in THF (500 μL) was added aqueous KOH (60 μL of a 1.039 N solution). The reaction mixture was stirred at room temperature for 1 h and then gently refluxed for 1 h. The reaction was cooled to 0°C and acidified to pH 6.0 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the free acid **219** which was used without further purification in the next reaction.

Example 85

(mono methyl) guanidino amino acid **220**: To a solution of (mono methyl) bis-Boc guanidnyl acid **219** (crude from previous reaction) in CH_2Cl_2 (1.0 mL) cooled to 0°C was added neat trifluoroacetic acid (1.0 mL). The reaction mixture was stirred at 0°C for 1 h and then at room temperature for 1 h. Concentration *in vacuo* gave a pale solid which was purified by C_{18} reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 4.4 mg (33%, 2 steps) of the guanidine carboxylic acid **220**. ^1H NMR (D_2O , 300 MHz): δ 6.52 (bs, 1H); 4.27 (bd, 1H, $J = 8.4$ Hz); 4.01 (dd, 1H, $J = 9.2, 10.3$ Hz); 3.86-3.75 (m, 1H); 3.75-3.67 (m, 1H); 3.60-3.49 (m, 1H); 2.85 (s, 3H); 2.80 (dd, 1H, $J = 5.1, 17.7$ Hz); 2.47-2.37 (m, 1H); 2.04 (s, 3H); 1.64-1.50 (m, 2H); 0.90 (t, 3H, $J = 7.2$ Hz).

Example 86

(R)-methyl propyl ester **221**: $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (63 μL , 0.51 mmol) was added to a solution of N-trityl aziridine **183** (150 mg, 0.341 mmol) in (R)-(-)-2-butanol (1.2 mL) under argon with stirring at room temperature. The pale solution was heated at 70°C for 2 h and then concentrated *in vacuo* to give a brown residue which was dissolved in dry pyridine (2.0 mL) and treated with acetic anhydride (225 μL) and a catalytic amount of DMAP (few crystals) at 0°C . The reaction was allowed to warm to room temperature and stirred for 2 h, concentrated *in vacuo* and partitioned between ethyl acetate and brine. The

organic layer was separated and washed sequentially with dilute HCl, saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (50% hexanes in ethyl acetate) gave 75 mg (72%) of the (R)-methyl propyl ester **221** as a pale solid. ¹H NMR (CDCl₃, 300 MHz): δ 6.79 (t, 1H, *J* = 2.2 Hz); 6.14 (d, 1H, *J* = 7.3 Hz); 4.55 (bd, 1H, *J* = 8.7 Hz); 4.33-4.23 (m, 1H); 3.77 (s, 3H); 3.56-3.45 (m, 1H); 3.40-3.27 (m, 1H); 2.85 (dd, 1H, *J* = 5.5, 17.5 Hz); 2.30-2.15 (m, 1H); 2.04 (s, 3H); 1.5901.40 (m, 2H); 1.10 (d, 3H, *J* = 6.0 Hz); 0.91 (t, 3H, *J* = 7.4 Hz).

Example 87

(R)-methyl propyl amino ester 222: Ph₃P (95 mg, 0.36 mmol) was added in one portion to a solution of azide **221** (75 mg, 0.24 mmol) and water (432 μL) in THF (3.0 mL). The pale yellow solution was then heated at 50°C for 10 h, cooled and concentrated *in vacuo* to give a pale solid. Purification by flash chromatography on silica gel (50% methanol in ethyl acetate) gave 66 mg (97%) of the amino ester **222** as a pale solid.

Example 88

Amino acid 223: A solution of methyl ester **222** (34 mg, 0.12 mmol) in THF (1.0 mL) was treated with aqueous KOH (175 μL of a 1.039 N solution). The reaction mixture was stirred at room temperature for 3 h and acidified to pH 6.0 with Amberlite IR-120 (H⁺) acidic resin. The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the amino acid as a pale solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 11.5 mg (36%) of the amino acid **223**. ¹H NMR (D₂O, 300 MHz): δ 6.52 (bs, 1H); 4.28 (bd, 1H, *J* = 8.7 Hz); 4.04 (dd, 1H, *J* = 8.8, 11.5 Hz); 3.74-3.65 (m, 1H); 3.50-3.60 (m, 1H); 2.90 (dd, 1H, *J* = 5.5, 17.2 Hz); 2.50-2.40 (m, 1H); 2.10 (s, 3H); 1.60-1.45 (m, 2H); 1.14 (d, 3H, *J* = 6.2 Hz); 0.91 (t, 3H, *J* = 7.4 Hz).

Example 89

bis-Boc guanidino ester 224: Treated according to the procedure of Kim and Qian, "Tetrahedron Lett.", 34:7677 (1993). To a solution of amine **222** (32 mg, 0.113 mmol), bis-Boc thiourea (32 mg, 0.115 mmol) and Et₃N (53 μL) in dry DMF (350 μL) cooled to 0°C was added HgCl₂ (34 mg, 0.125 mmol) in one portion. The heterogeneous reaction mixture was stirred for 45 min at 0°C and then at room temperature for 1 h, after which the reaction was diluted with EtOAc and filtered through a pad of celite. Concentration *in vacuo*

followed by flash chromatography of the residue on silica gel (20% hexanes in ethyl acetate) gave 57 mg (96%) of **224** as a colorless foam. ¹H NMR (CDCl₃, 300 MHz): δ 11.40 (s, 1H); 8.65 (d, 1H, *J* = 7.8 Hz); 6.82 (s, 1H); 6.36 (d, 1H, *J* = 8.7 Hz); 4.46-4.34 (m, 1H); 4.20-4.10 (m, 1H); 4.10-3.95 (m, 1H); 3.76 (s, 3H); 2.79 (dd, 1H, *J* = 5.4, 17.7 Hz); 2.47-2.35 (m, 1H); 1.93 (s, 3H); 1.60-1.45 (m, 2H); 1.49 (s, 18H); 1.13 (d, 3H, *J* = 6.0 Hz); 0.91 (t, 3H, *J* = 7.5 Hz).

Example 90

Carboxylic acid 225: To a solution of methyl ester **224** (57 mg, 0.11 mmol) in THF (1.5 mL) was added aqueous KOH (212 μL of a 1.039 N solution). The reaction mixture was stirred at room temperature for 16 h, cooled to 0°C and acidified to pH 4.0 with Amberlite IR-120 (H⁺) acidic resin. The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the free acid as a pale foam which was used without further purification in the next reaction.

Example 91

Guanidine carboxylic acid 226: To a solution of bis-Boc guanidnyl acid **225** (crude from previous reaction) in CH₂Cl₂ (4.0 mL) cooled to 0°C was added neat trifluoroacetic acid (4.0 mL). The reaction mixture was stirred at 0°C for 1 h and then at room temperature for 2 h. Concentration *in vacuo* gave a pale orange solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 18.4 mg (40%, 2 steps) of the guanidine carboxylic acid **226**. ¹H NMR (D₂O, 300 MHz): δ 6.47 (s, 1H); 4.28 (bd, 1H, *J* = 8.4 Hz); 3.93-3.74 (m, 2H); 3.72-3.63 (m, 1H); 2.78 (dd, 1H, *J* = 4.8, 17.4 Hz); 2.43-2.32 (m, 1H); 1.58-1.45 (m, 2H); 1.13 (d, 3H, *J* = 6.0 Hz); 0.90 (t, 3H, *J* = 7.4 Hz).

Example 92

(Diethyl) methyl ether ester 227: BF₃•Et₂O (6.27 mL, 51 mmol) was added to a solution of N-trityl aziridine **183** (15 g, 34 mmol) in 3-pentanol (230 mL) under argon with stirring at room temperature. The pale solution was heated at 70-75°C for 1.75 h and then concentrated *in vacuo* to give a brown residue which was dissolved in dry pyridine (2.0 mL) and treated with acetic anhydride (16 mL, 170 mmol) and a catalytic amount of DMAP 200 mg. The reaction was stirred at room temperature for 18 h, concentrated *in vacuo* and partitioned between ethyl acetate and 1M HCl. The organic layer was separated and washed sequentially with saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration *in vacuo* followed by flash

chromatography of the residue on silica gel (50% hexanes in ethyl acetate) gave 7.66 g of the (Diethyl) methyl ether ester which was recrystallized from ethylacetate/hexane to afford 227 (7.25 g, 66%) as colorless needles: ^1H NMR (CDCl_3 , 300 MHz): δ 6.79 (t, 1H, $J = 2.1$ Hz); 5.92 (d, 1H, $J = 7.5$ Hz); 4.58 (bd, 1H, $J = 8.7$ Hz); 4.35-4.25 (m, 1H); 3.77 (s, 3H); 3.36-3.25 (m, 2H); 2.85 (dd, 1H, $J = 5.7$, 17.4 Hz); 2.29-2.18 (m, 1H); 2.04 (s, 3H); 1.60-1.45 (m, 4H); 0.91 (t, 3H, $J = 3.7$ Hz); 0.90 (t, 3H, $J = 7.3$ Hz).

Example 93

(Diethyl) methyl ether amino ester 228: Ph_3P (1.21 g, 4.6 mmol) was added in one portion to a solution of azide 227 (1 g, 3.1 mmol) and water (5.6 mL) in THF (30 mL). The pale yellow solution was then heated at 50°C for 10 h, cooled and concentrated *in vacuo*. The aqueous oily residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried (MgSO_4), filtered, and evaporated. Purification by flash chromatography on silica gel (50% methanol in ethyl acetate) gave 830 mg (90%) of the amino ester 228 as a pale white solid. ^1H NMR (CDCl_3 , 300 MHz): δ 6.78 (t, 1H, $J = 2.1$ Hz); 5.68 (bd, 1H, $J = 7.8$ Hz); 4.21-4.18 (m, 1H); 3.75 (s, 3H); 3.54-3.45 (m, 1H); 3.37-3.15 (m, 2H); 2.74 (dd, 1H, $J = 5.1$, 17.7 Hz); 2.20-2.07 (m, 1H); 2.03 (s, 3H); 1.69 (bs, 2H, $-\text{NH}_2$); 1.57-1.44 (m, 4H); 0.90 (t, 3H, $J = 7.5$ Hz); 0.89 (t, 3H, $J = 7.5$ Hz).

Example 94

Amino acid 229: A solution of methyl ester 228 (830 mg, 2.8 mmol) in THF (15 mL) was treated with aqueous KOH (4 mL of a 1.039 N solution). The reaction mixture was stirred at room temperature for 40 min and acidified to pH 5.5-6.0 with Dowex 50WX8 acidic resin. The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the amino acid as a pale solid which was purified by C₁₈ reverse phase chromatography eluting with water and then with 5% CH₃CN/water. Fractions containing the desired product were pooled and lyophilized to give 600 mg (75%) of the amino acid 229. ¹H NMR (D₂O, 300 MHz): δ 6.50 (t, 1H, *J* = 2.1 Hz); 4.30-4.26 (m, 1H); 4.03 (dd, 1H, *J* = 9.0, 11.7 Hz); 3.58-3.48 (m, 2H); 2.88 (dd, 1H, *J* = 5.4, 16.8 Hz); 2.53-2.41 (m, 1H); 1.62-1.40 (m, 4H); 0.90 (t, 3H, *J* = 7.5 Hz); 0.85 (t, 3H, *J* = 7.5 Hz).

Example 95

t-amyl ether ester 230: BF₃•Et₂O (43 μL, 0.35 mmol) was added to a solution of N-trityl aziridine 183 (104 mg, 0.24 mmol) in *t*-amyl alcohol (2.5 mL) under argon with stirring at room temperature. The pale solution was heated at 75°C for 3 h and then concentrated *in vacuo* to give a brown residue which was dissolved in dry pyridine (2.0 mL) and treated with acetic anhydride (250 μL) and a catalytic amount of DMAP (few crystals). The reaction was stirred at room temperature for 1.5 h, concentrated *in vacuo* and partitioned between ethyl acetate and brine. The organic layer was separated and washed sequentially with dilute HCl, saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (50% hexanes in ethyl acetate) gave 27 mg (35%) of the *t*-amyl ether ester 230 as a pale orange oil. ¹H NMR (CDCl₃, 300 MHz): δ 6.72 (t, 1H, *J* = 2.1 Hz); 5.83 (d, 1H, *J* = 7.2 Hz); 4.71 (bd, 1H, *J* = 8.1 Hz); 4.45-4.35 (m, 1H); 3.75 (s, 3H); 3.27-3.17 (m, 1H); 2.84 (dd, 1H, *J* = 5.7, 17.4 Hz); 2.27-2.15 (m, 1H); 2.05 (s, 3H); 1.57-1.47 (m, 2H); 1.19 (s, 3H); 1.15 (s, 3H); 0.90 (t, 3H, *J* = 7.5 Hz).

Example 96

t-amyl ether amino ester 231: Ph₃P (35 mg, 0.133 mmol) was added in one portion to a solution of azide 230 (27 mg, 0.083 mmol) and water (160 μL) in THF (1.5 mL). The pale orange solution was then heated at 50°C for 10 h, cooled and concentrated *in vacuo* to give a pale solid. Purification by flash

chromatography on silica gel (50% methanol in ethyl acetate) gave 20 mg (82%) of the amino ester 231 as a pale oil.

Example 97

Amino acid 232: A solution of methyl ester 231 (20 mg, 0.068 mmol) in THF (1.0 mL) was treated with aqueous KOH (131 μ L of a 1.039 N solution). The reaction mixture was stirred at room temperature for 2.5 h and acidified to pH 5.0 with Amberlite IR-120 (H⁺) acidic resin. The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the amino acid as a pale solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 8.6 mg (45%) of the amino acid 232. ¹H NMR (D₂O, 300 MHz): δ 6.47 (bs, 1H); 4.42 (bd, 1H, *J* = 8.1 Hz); 3.97 (dd, 1H, *J* = 8.4, 11.4 Hz); 3.65-3.54 (m, 1H); 2.88 (dd, 1H, *J* = 5.5, 17.3 Hz); 2.51-2.39 (m, 1H); 2.08 (s, 3H); 1.61-1.46 (m, 2H); 1.23 (s, 3H); 1.18 (s, 3H), 0.86 (t, 3H, *J* = 7.5 Hz).

Example 98

***n*-Propyl thio ether ester 233:** BF₃•Et₂O (130 μ L, 1.06 mmol) was added to a solution of N-trityl aziridine 183 (300mg, 0.68 mmol) in 1-propanethiol (8.0 mL) under argon with stirring at room temperature. The pale solution was then heated at 65°C for 45 min, concentrated and partitioned between ethyl acetate and brine. The organic layer was separated and washed with saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (30% hexanes in ethyl acetate) gave 134 mg (73%) of the *n*-propyl thio ether ester 233 as a pale oil. ¹H NMR (CDCl₃, 300 MHz): δ 6.87 (t, 1H, *J* = 2.4 Hz); 3.77 (s, 3H); 3.48-3.38 (m, 1H); 3.22-3.18 (m, 1H), 2.93 (dd, 1H, *J* = 5.4, 17.4 Hz); 2.80 (t, 1H, *J* = 9.9 Hz); 2.51 (t, 2H, *J* = 7.2 Hz); 2.32-2.20 (m, 1H); 1.96 (bs, 2H, -NH₂), 1.69-1.56 (m, 2H); 1.00 (t, 3H, *J* = 7.2 Hz).

Example 99

***n*-Propyl thio ether azido ester 234:** To a solution of amine 233 (134 mg, 0.50 mmol) in pyridine (1.5 mL) cooled to 0°C was added neat acetyl chloride (60 μ L, 0.84 mmol). After stirring for 1 h the reaction mixture was warmed to room temperature and stirred for an additional 15 min. The reaction was concentrated and partitioned between ethyl acetate and brine and washed sequentially with dilute HCl, water, saturated sodium bicarbonate, brine and dried over MgSO₄. Concentration *in vacuo* followed by flash chromatography

of the residue on silica gel (30% hexanes in ethyl acetate) gave 162 mg (100%) of the *n*-Propyl thio ether azido ester **234** as a pale yellow solid. ¹H NMR (CDCl₃, 300 MHz): δ 6.90 (t, 1H, *J* = 2.7 Hz); 5.87 (bd, 1H, *J* = 7.8 Hz); 4.07-3.98 (m, 1H); 3.77 (s, 3H); 3.65-3.55 (m, 1H); 2.95-2.85 (m, 1H); 2.60-2.45 (m, 2H); 2.30-2.18 (m, 1H); 2.08 (s, 3H); 1.65-1.53 (m, 2H); 0.98 (t, 3H, *J* = 7.2 Hz).

Example 100

***n*-Propyl thio ether amino ester 235:** The azide **234** (130 mg, 0.416 mmol) in ethyl acetate (10 mL) was hydrogenated (1 atmosphere) over Lindlar's catalyst (150 mg) for 18 h at room temperature. The catalyst was then filtered through a celite pad and washed with hot ethyl acetate and methanol. Concentration *in vacuo* followed by flash chromatography of the orange residue gave 62 mg (53%) of the *n*-propyl thio ether amino ester **235**. ¹H NMR (CDCl₃, 300 MHz): δ 6.88 (t, 1H, *J* = 2.7 Hz); 5.67 (bd, 1H, *J* = 8.7 Hz); 3.76 (s, 3H); 3.75-3.65 (m, 1H); 3.45-3.35 (bm, 1H); 3.05-2.95 (m, 1H); 2.87-2.78 (m, 1H); 2.56-2.40 (m, 2H); 2.18-2.05 (m, 1H); 2.09 (s, 3H); 1.65-1.50 (m, 2H); 1.53 (bs, 2H, -NH₂); 0.98 (t, 3H, *J* = 7.2 Hz).

Example 101

Compound 240: A suspension of Quinic acid (103 g), 2,2-dimethoxypropane (200 mL) and toluenesulfonic acid (850 mg) in acetone (700 mL) was stirred at room temperature for 4 days. Solvents and excess reagents were removed under reduced pressure. Purification by flash column chromatography (Hexanes/EtOAc = 2/1-1.5/1) gave lactone **240** (84 g, 73%): ¹H NMR (CDCl₃) δ 4.72 (dd, *J* = 2.4, 6.1 Hz, 1 H), 4.50 (m, 1 H), 4.31 (m, 1 H), 2.67 (m, 2 H), 2.4-2.2 (m, 3 H), 1.52 (s, 3 H), 1.33 (s, 3 H). Performing the reaction at reflux temperatures for 4 h afforded lactone **240** in 71% yield after aqueous work-up (ethyl acetate/water partition) and recrystallization of the crude product from ethyl acetate/hexane.

Example 102

Compound 241: To a solution of lactone **240** (43.5 g, 203 mmol) in methanol (1200 mL) was added sodium methoxide (4.37 M, 46.5 mL, 203 mmol) in one portion. The mixture was stirred at room temperature for 3 hrs, and quenched with acetic acid (11.62 mL). Methanol was removed under reduced pressure. The mixture was diluted with water, and extracted with EtOAc (3x). The combined organic phase was washed with water (1x) and brine (1x), and dried over MgSO₄. Purification by flash column

chromatography (Hexanes/EtOAc = 1/1 to 1/4) gave diol (43.4g, 87%): ^1H NMR (CDCl_3) δ 4.48 (m, 1 H), 4.13 (m, 1 H), 3.99 (t, J = 6.4 Hz, 1 H), 3.82 (s, 3 H), 3.34 (s, 1 H), 2.26 (d, J = 3.8 Hz, 2 H), 2.08 (m, 1 H), 1.91 (m, 1 H), 1.54 (s, 3 H), 1.38 (s, 3 H). Alternatively, treatment of lactone 240 with catalytic sodium ethoxide (1 mol%) in ethanol gave the corresponding ethyl ester in 67% after crystallization of the crude product from ethyl acetate/hexane. The residue obtained from the mother liquor (consisting of starting material and product) was subjected again to the same reaction conditions, affording additional product after recrystallization. Overall yield was 83%.

10 Example 103

Compound 242: To a solution of diol 241 (29.8 g, 121 mmol) and 4-(N,N-dimethylamino)pyridine (500 mg) in pyridine (230 mL) was added tosyl chloride (27.7 g, 145 mmol). The mixture was stirred at room temperature for 3 days, and pyridine was removed under reduced pressure. The mixture was diluted with water, and extracted with EtOAc (3x). The combined organic phase was washed with water (2x) and brine (1x), and dried over MgSO_4 . Concentration and purification by flash column chromatography (Hexanes/EtOAc = 2/1-1/1) gave tosylate 242 (44.6 g, 92%): ^1H NMR (CDCl_3) δ 7.84 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 8.1 Hz, 2 H), 4.76 (m, 1 H), 4.42 (m, 1 H), 4.05 (dd, J = 5.5, 7.5 Hz, 1 H), 3.80 (s, 3 H), 2.44 (s, 3 H), 2.35 (m, 1 H), 2.24 (m, 2 H), 1.96 (m, 1 H), 1.26 (s, 3 H), 1.13 (s, 3 H). The corresponding ethyl ester of compound 241 was treated with methanesulfonyl chloride and triethylamine in CH_2Cl_2 at 0°C to afford the mesylate derivative in quantitative yield after aqueous work-up. The mesylate was used directly without any further purification.

Example 104

Compound 243: To a solution of tosylate 242 (44.6 g, 111.5 mmol) in CH_2Cl_2 (450 mL) at -78°C was added pyridine (89 mL), followed by slow addition of SO_2Cl_2 (26.7 mL, 335 mmol). The mixture was stirred at -78°C for 5 hrs, and methanol (45 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 12 hrs. Ethyl ether was added, and the mixture was washed with water (3x) and brine (1x), and dried over MgSO_4 . Concentration gave the intermediate as a oil (44.8 g). To a solution of the intermediate (44.8 g, 111.5 mmol) in MeOH (500 mL) was added TsOH (1.06 g, 5.6 mmol). The mixture was refluxed for 4 hrs. The reaction mixture was cooled to room temperature, and methanol was removed under reduced

pressure. Fresh methanol (500 mL) was added, and the whole mixture was refluxed for another 4 hrs. The reaction mixture was cooled to room temperature, and methanol was removed under reduced pressure. Purification by flash column chromatography (Hexanes/EtOAc = 3/1-1/3) gave a mixture of the two isomers (26.8 g). Recrystallization from EtOAc/Hexanes afforded the pure desired product **243** (20.5 g, 54%): ¹H NMR (CDCl₃) δ 7.82 (d, J = 8.3 Hz, 2 H), 7.37 (d, J = 8.3 Hz, 2 H), 6.84 (m, 1 H), 4.82 (dd, J = 5.8, 7.4 Hz, 1 H), 4.50 (m, 1 H), 3.90 (dd, J = 4.4, 8.2 Hz, 1 H), 3.74 (s, 3 H), 2.79 (dd, J = 5.5, 18.2 Hz, 1 H), 2.42 (dd, J = 6.6, 18.2 Hz, 1 H). The corresponding mesylate-ethyl ester derivative of compound **242** was treated in the same manner as described. Removal of the acetonide protecting group was accomplished with acetic acid in refluxing ethanol to afford the diol in 39% yield by direct precipitation with ether from the crude reaction mixture.

Example 105

Compound 1: To a solution of diol **243** (20.0 g, 58.5 mmol) in THF (300 mL) at 0°C was added DBU (8.75 mL, 58.5 mmol). The reaction mixture was warmed to room temperature, and stirred for 12 hrs. Solvent (THF) was removed under reduced pressure. Purification by flash column chromatography (Hexanes/EtOAc = 1/3) gave epoxide **1** (9.72 g, 100%): ¹H NMR (CDCl₃) δ 6.72 (m, 1 H), 4.56 (td, J = 2.6, 10.7 Hz, 1 H), 3.76 (s, 3 H), 3.56 (m, 2 H), 3.0 (d, J = 21 Hz, 1 H), 2.50 (d, J = 20 Hz, 1 H), 2.11 (d, 10.9 Hz, 1 H). The corresponding mesylate-ethyl ester derivative of compound **243** was treated in the same manner as described, affording the epoxide in nearly quantitative yield.

Example 106

Aziridine 244: A solution of allyl ether **4** (223 mg, 1.07 mmol) and Lindlar's catalyst (200 mg) in absolute ethanol (8.0 mL) was treated with hydrogen gas (1 atmosphere) at room temperature for 50 min. The catalyst was then filtered through a celite pad and washed with hot methanol. Concentration *in vacuo* gave ~230 mg of **244** as pale yellow oil which was used for the next reaction without any further purification.

Example 107

Azido amine 205: Crude aziridine **244** (230 mg), sodium azide (309 mg, 4.75 mmol) and ammonium chloride (105 mg, 1.96 mmol) in dry DMF (10 mL) was heated at 70°C for 16 h under an argon atmosphere. The reaction

was cooled, filtered through a fritted glass funnel to remove solids and partitioned between ethyl acetate and brine. The organic layer was separated and dried over MgSO_4 . Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (10% hexanes in ethyl acetate) gave 154 mg (57%, 2 steps) of 205 as a yellow viscous oil of sufficient purity for the next reaction.

Example 108

N-acetyl azide 245: Acetyl chloride (70 μL , 0.98 mmol) was added to a solution of amine 205 (154 mg, 0.61 mmol) and pyridine (1.3 mL) in CH_2Cl_2 (4.0 mL) cooled to 0°C . After 1.5 h at 0°C the reaction was concentrated and partitioned between ethyl acetate and brine. The organic layer was separated and washed sequentially with saturated sodium bicarbonate, brine and dried over MgSO_4 . Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (ethyl acetate) gave 167 mg (93%) of 245 as a pale yellow solid.

Example 109

Amino ester 200: Triphenyl phosphine (1.7 g, 6.48 mmol) was added in several portions to a solution of 245 (1.78 g, 6.01 mmol) in THF (40 mL) and water (1.5 mL). The reaction was then stirred at room temperature for 42.5 h. Volatiles were removed under vacuum and the crude solid absorbed onto silica gel and purified by flash chromatography on silica gel (100% ethyl acetate then 100% methanol) to give 1.24 g (77%) of 200 as a pale solid.

Example 110

Amino acid 102: To a solution of methyl ester 200 (368 mg, 1.37 mmol) in THF (4.0 mL) cooled to 0°C was added aqueous NaOH (1.37 mL of a 1.0 N solution). The reaction mixture was stirred at 0°C for 10 min, room temperature for 1.5 h and then acidified to pH 7.0-7.5 with Amberlite IR-120 (H^+) acidic resin. The resin was filtered and washed with water and methanol. Concentration *in vacuo* gave the amino acid as a white solid which was purified by C_{18} reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 290 mg (83%) of amino acid 102.

Example 111

Amine hydrochloride 250: Amine 228 (15.6 mg, 0.05 mmol) was treated with 0.1 N HCl and was evaporated. The residue was dissolved in water and

was filtered through a small column of C-18 reverse phase silica gel. The hydrochloride salt 250 (12 mg) was obtained as a solid after lyophilization: ^1H NMR (D_2O) δ 6.86 (s, 1H), 4.35 (br d, $J = 9.0$), 4.06 (dd, 1H, $J = 9.0, 11.6$), 3.79 (s, 3H), 3.65-3.52 (m, 2H), 2.97 (dd, 1H, $J = 5.5, 17.2$), 2.58-2.47 (m, 1H), 2.08 (s, 3H), 1.61-1.41 (m, 4H), 0.88 (t, 3H, $J = 7.4$), 0.84 (t, 3H, $J = 7.4$).

Example 112

Bis-Boc-guanidine 251: To a solution of amine 228 (126 mg, 0.42 mmol), *N, N'*-bis-*tert*-butoxycarbonylthiourea (127 mg, 0.46 mmol), and triethylamine (123 μL , 0.88 mmol) in DMF (4 mL) at 0°C was added HgCl_2 (125 mg, 0.46 mmol). The mixture was stirred at 0°C for 30 min and at room temperature for 1.5 h. The reaction was diluted with ethyl acetate and filtered through celite. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with saturated NaCl, dried (MgSO_4), filtered and the solvent was evaporated. The crude product was purified on silica gel (2/1, 1/1-hexane/ethyl acetate) to afford bis-Boc-guanidine 251 (155 mg, 69%) as a solid: ^1H NMR (CDCl_3) δ 11.40 (s, 1H), 8.66 (d, 1H, $J = 7.9$), 6.8 (s, 1H), 6.22 (d, 1H, $J = 8.9$), 4.43-4.34 (m, 1H), 4.19-4.08 (m, 1H), 4.03 (m, 1H), 3.76 (s, 3H), 3.35 (m, 1H), 2.79 (dd, 1H, $J = 5.4, 17.7$), 2.47-2.36 (m, 1H), 1.92 (s, 3H), 1.50, 1.49 (2s, 18H), 0.89 (m, 6H).

Example 113

Guanidino-acid 252: To a solution of bis-Boc-guanidine 251 (150 mg, 0.28 mmol) in THF (3 mL) was added 1.039N KOH solution (337 μL) and water (674 μL). The mixture was stirred for 3 h, additional 1.039N KOH solution (67 μL) was added and stirring was continued for 2 h. The reaction was filtered to remove a small amount of dark precipitate. The filtrate was cooled to 0°C and was acidified with IR 120 ion exchange resin to pH 4.5-5.0. The resin was filtered and washed with methanol. The filtrate was evaporated to a residue which was dissolved in CH_2Cl_2 (3 mL), cooled to 0°C , and was treated with trifluoroacetic acid (3 mL). After stirring 10 min. at 0°C , the reaction was stirred at room temperature for 2.5 h. The solvents were evaporated and the residue was dissolved in water and was chromatographed on a short column (3X1.5 cm) of C-18 reverse phase silica gel eluting initially with water and then 5% acetonitrile/water. Product fractions were combined and evaporated. The residue was dissolved in water and lyophilized to afford guanidino-acid 252 (97 mg, 79%) as a white solid.

Example 114

Azido acid 260: To a solution of methyl ester 227 (268 mg, 0.83 mmol) in THF (7.0 mL) was added aqueous KOH (1.60 mL of a 1.039 N solution) at room temperature. After stirring for 19 h at room temperature the reaction was acidified to pH 4.0 with Amberlite IR-120 (H⁺) acidic resin. The resin was filtered and washed with water and ethanol. Concentration *in vacuo* gave the crude azido acid 260 as a pale orange foam which was used for the next reaction without any further purification.

Example 115

Azido ethyl ester 261: To a solution of carboxylic acid 260 (crude from previous reaction, assume 0.83 mmol), ethyl alcohol (150 μ L), and catalytic DMAP in CH₂Cl₂ (6.0 mL) was added DCC (172 mg, 0.83 mmol) in one portion at room temperature. After several minutes a precipitate formed and after an additional 1 h of stirring the reaction was filtered and washed with CH₂Cl₂. Concentration *in vacuo* afforded a pale solid which was purified by flash chromatography on silica gel (50% hexanes in ethyl acetate) to give 272 mg (96%, small amount of DCU impurity present) of 261 as a white solid. When DCC was replaced by diisopropyl carbodiimide than the yield of 261 was 93% but the chromatographic purification eliminated urea impurities present when DCC was used.

Example 116

Amino ethyl ester 262: Triphenyl phosphine (342 mg, 1.30 mmol) was added in one portion to a solution of 261 (272 mg, 0.80 mmol) in THF (17 mL) and water (1.6 mL). The reaction was then heated at 50°C for 10 h, cooled and concentrated *in vacuo* to give a pale white solid. Purification of the crude solid by flash chromatography on silica gel (50% methanol in ethyl acetate) gave 242 mg (96%) of the amino ethyl ester 262 as a pale solid. The amino ethyl ester is dissolved in 3N HCl and lyophilized to give the corresponding water soluble HCl salt form. ¹H NMR (D₂O, 300 MHz): δ 6.84 (s, 1H); 4.36-4.30 (br m, 1H); 4.24 (q, 2H, *J* = 7.2 Hz); 4.05 (dd, 1H, *J* = 9.0, 11.7 Hz); 3.63-3.50 (m, 2H); 2.95 (dd, 1H, *J* = 5.7, 17.1 Hz); 2.57-2.45 (m, 1H); 1.60-1.39 (m, 4H); 1.27 (t, 3H, *J* = 7.2 Hz); 0.89-0.80 (m, 6H).

Example 117

bis-Boc guanidino ethyl ester 263: Treated according to the procedure of Kim and Qian, "Tetrahedron Lett." 34:7677 (1993). To a solution of amine 262

(72 mg, 0.23 mmol), bis-Boc thiourea (66 mg, 0.24mmol) and Et₃N (108 μ L) in dry DMF (600 μ L) cooled to 0°C was added HgCl₂ (69 mg, 0.25mmol) in one portion. The heterogeneous reaction mixture was stirred for 1 h at 0°C and then at room temperature for 15 min, after which the reaction was diluted with EtOAc and filtered through a pad of celite. Concentration *in vacuo* followed by flash chromatography of the residue on silica gel (20% hexanes in ethyl acetate) gave 113 mg (89%) of **263** as a colorless foam. ¹H NMR (CDCl₃, 300 MHz): δ 11.41 (s, 1H); 8.65 (d, 1H, *J* = 8.1 Hz); 6.83 (s, 1H); 6.22 (d, 1H, *J* = 9.0 Hz); 4.46-4.34 (m, 1H); 4.21 (q, 2H, *J* = 6.9 Hz); 4.22-4.10 (m, 1H); 4.04-4.00 (m, 1H); 3.36 (quintet, 1H, *J* = 5.7 Hz); 2.78 (dd, 1H, *J* = 5.4, 17.7 Hz); 2.46-2.35 (m, 1H); 1.94 (s, 3H); 1.60-1.40 (m, 4H); 1.49 (s, 9H); 1.50 (s, 9H); 1.30 (t, 3H, *J* = 6.9 Hz); 0.93-0.84 (m, 6H).

Example 118

Guanidino ethyl ester 264: To a solution of bis-Boc guanidnyl ethyl ester **263** (113 mg, 0.20 mmol) in CH₂Cl₂ (5.0 mL) cooled to 0°C was added neat trifluoroacetic acid (5.0 mL). The reaction mixture was stirred at 0°C for 30 min and then at room temperature for 1.5 h. The reaction was then concentrated *in vacuo* to give a pale orange solid which was purified by C₁₈ reverse phase chromatography eluting with water. Fractions containing the desired product were pooled and lyophilized to give 63 mg (66%) of the guanidine ethyl ester **264** as white solid. ¹H NMR (D₂O, 300 MHz): δ 6.82 (s, 1H); 4.35-4.31 (m, 1H); 4.24 (q, 2H, *J* = 7.1 Hz); 3.95-3.87 (m, 1H); 3.85-3.76 (m, 1H); 3.57-3.49 (m, 1H); 2.87 (dd, 1H, *J* = 5.1, 17.7 Hz); 2.46-2.34 (m, 1H); 2.20 (s, 3H); 1.60-1.38 (m, 4H); 1.28 (t, 3H, *J* = 7.1 Hz); 0.90-0.80 (m, 6H).

Example 119

Enzyme Inhibition: Using the methods of screening *in vitro* activity described above, the following activities were observed (+ 10-100 μm , ++ 1-10 μm , +++ <1.0 μm):

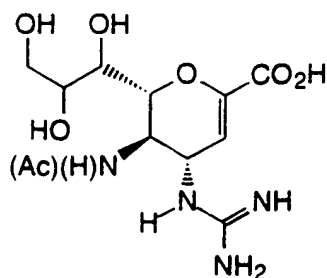
Compound	IC ₅₀
102/103 (2:1)	+++
8	++
A.17.a.4.i	++
114	++
A.1.a.4.i	++
79	+
82/75 (1.2:1)	+
94	+++
A.100.a.11.i	+++
A.101.a.11.i	+++
A.113.a.4.i	+++

Example 120

Compounds A.113.b.4.i and A.113.x.4.i were incubated separately in enzyme assay buffey and tested for activity as described in Example 119. Activity was >100 μm for both. When each compound was separately incubated in rat plasma prior to testing as described in Example 119, activity of both was similar to compound A.113.a.4.i.

Example 121

Studies were conducted under the supervision of Dr. Robert Sidwell at the Institute for Antiviral Research of Utah State University to determine the comparative anti-influenza A activity of compound 203 (example 69), GG167 and ribavirin in vivo in mice by i.p. or p.o. routes of administration. GG167 and ribavirin are known anti-influenza virus compounds.

**GG167**

Mice: Female 13-15 g specific-pathogen free BALB/c mice were obtained from Simonsen Laboratories (Gilroy, CA). They were quarantined 24 hr prior to use, and maintained on Wayne Lab Blox and tap water. Once infected, the drinking water contained 0.006% oxytetracycline (Pfizer, New York, NY) to control possible secondary bacterial infections.

Virus: Influenza A/NWS/33 (H1N1) was obtained from K.W. Cochran, University of Michigan (Ann Arbor, MI). A virus pool was prepared by infecting confluent monolayers of Madin Darby canine kidney (MDCK) cells, incubating them at 37°C in 5% CO₂, and harvesting the cells at 3 to 5 days when the viral cytopathic effect was 90 to 100%. The virus stock was ampuled and stored at -80°C until used.

Compounds: Compound 203 and GG167 were dissolved in sterile physiological saline for this study.

Arterial Oxygen Saturation (SaO₂) Determinations: SaO₂ was determined using the Ohmeda Biox 3740 pulse oximeter (Ohmeda, Louisville, OH). The ear probe attachment was used, the probe placed on the thigh of the animal, with the slow instrument mode selected. Readings were made after a 30 second stabilization time on each animal. Use of this device for measuring effects of influenza virus on arterial oxygen saturation has been described by Sidwell et al., *Antimicrob. Agents Chemother.* 36:473-476 (1992).

Experiment Design for Oral Administration Study: Groups of eleven mice infected intranasally with an approximate 95% lethal dose of virus received each dose of test compound. Doses of both 203 and GG167 were 50, 10, 2 and 0.5 mg/kg/day. Treatments were i.p. twice daily for 5 days beginning 4 hr pre-virus exposure. Eight of the infected, treated mice at each dosage and 16 infected, saline-treated controls were assayed for SaO₂ level on days 3 through 10; deaths were recorded daily in these animals for 21 days. The remaining three animals in each group as well as six saline-treated control

mice were killed on day 6 and their lungs removed, weighed, assigned a consolidation score based on extent of plum color in the lungs (0=normal, 4=100% of lung affected). Since no toxicity had been seen at a dose of 300 mg/kg/day of 203 and literature reports indicate GG167 to be similarly nontoxic, toxicity controls were not included in this study.

Experiment Design for Intraperitoneal Administration Study: Groups of 11 mice were infected intranasally with an approximate 95% lethal dose of virus and treated with 250, 50, or 10 mg/kg/day of 203 or GG167 or with 100, 32 or 10 mg/kg/day of ribavirin. Treatment was by oral gavage (p. o.) twice daily for 5 days beginning 4 hr pre-virus exposure. Eight of the animals in each group were held for 21 days, with deaths noted daily and SaO₂ levels determined on days 3-10. The remaining 3 infected mice in each group were killed on day 6 and their lungs removed, weighed, assigned a consolidation score of 0 (normal) to 4 (100% lung affected). Fifteen infected mice were treated with saline only and held 21 days with SaO₂ determined as above, and 6 additional infected, saline treated mice were killed on day 6 for lung assay. Three normal controls were held 21 days, with SaO₂ determined in parallel with the above, and an additional 3 normal animals were killed on day 6 for lung weight and score.

Experiment Design for Low Dose Oral Administration Study: Groups of 8 mice infected intranasally with an approximate 90% lethal concentration of virus received each dosage of compound. Doses of each compound were 10, 1, and 0.1 mg/kg/day. Treatments were p.o. twice daily for 5 days beginning 4 hr pre-virus exposure. Eight of the infected, treated mice at each dosage and 16 infected, saline-treated controls were assayed for SaO₂ level on days 3 through 11; deaths were recorded daily in these animals for 21 days.

Statistical Evaluation: Increase in survivor number was evaluated by chi square analysis with Yates' correction. Mean survival time increases and differences in SaO₂, lung weight and lung virus titers were analyzed by *t*-test. Lung score differences were evaluated by ranked sum analysis. In all cases, differences between drug-treated and saline-treated controls were studied.

The results of the i.p. dosing experiment are summarized in Table I and in Figures 1 and 2. While in this model both compounds were significantly inhibitory at the high dose used, 203 treatment also resulted in significant survivors at a dose of 10 mg/kg/day. SaO₂ decline was particularly inhibited by both compounds at the 50 mg/kg/day dose, and again GG167 appeared to

also prevent this decline at 10 and even 2 mg/kg/day. The lung score data appear to show the same trend of GG167 being effective at more than one dose. Some erraticism was seen in lung weights, with lungs taken from the mice receiving the highest dose of GG167 having a greater mean weight than the saline-treated controls.

The p.o. dosing study is summarized in Table II, with daily SaO₂ values shown in Figures 3-5. Oral treatment with all three drugs in this model was significantly inhibitory to the influenza virus infection, preventing death, lowering lung scores and infection-associated lung weights, and inhibiting the usual decline in SaO₂.

The p.o. low dose study results are summarized in Table III and in Figures 6-8. In this experiment, the infection was lethal to 14 of 16 saline-treated animals, the mean survival time being 9.6 days in this group. While all three compounds exhibited some degree of inhibitory effect on the virus infection, 262 (the ethyl ester prodrug) was the most effective at every dose as evidenced by number of survivors, mean survival time, and prevention of SaO₂ decline.

Table III shows the mean SaO₂% for all assay time taken together. The daily values for each compound are graphically represented in Figures 6 through 8. Figure 6 illustrates the SaO₂ data with the highest concentrations of each compound; Figure 7 shows the values at the median dose of each compound, and the SaO₂ values for the low dose of each compound are compared in Figure 8.

Table III and Figs. 6-8 indicate that while all three compounds were active orally against an experimentally induced influenza A (H1N1) virus infection, 262 was considered most effective. It was not determined whether the improved antiviral potency of 262 was unaccompanied with a concomitant increased animal toxicity, but this is unlikely since its greater efficacy is expected to be a result of its elevated oral bioavailability.

Table I. Comparison of the Effect of 203 and GG167 Administered i.p.^a to Influenza A (H1N1) Virus-Infected Mice

Compound	Dosage (mg/kg/day)	Surv./ Total	Mean Surv. Time ^b (days)	Mean SaO ₂ ^c %	Infected, Treated Mean Lung Parameters ^d	
					Score	Weight mg
203	50	8/8**	>21.0**	87.2**	0.7*	173*
	10	3/8*	10.8	84.7	2.5	217
	2	0/7	12.6	84.4	2.0	203
	0.5	0/8	11.1	85.2*	2.0	230
GG167	50	8/8**	>21.0**	87.6**	0.7*	230
	10	7/8**	15.0	87.5**	1.7	170*
	2	1/8	12.6	86.0**	1.3	213
	0.5	0/8	12.3	84.5	2.3	227
Saline	-	0/16	11.0	82.9	2.0	220

Table II. Comparison of the Effect of Orally Administered^a 203, GG167 and Ribavirin on Influenza A (H1N1) Virus Infections in Mice.

Compound	Dosage (mg/kg/day)	Surv./ Total	Mean Surv. ^b Time (days)	Mean SaO ₂ ^c %	Infected, Treated Mean Lung Parameters ^d	
					Score	Weight (mg)
203	250	8/8**	>21.0**	87.9*	0.8**	160**
	50	8/8**	>21.0**	87.9*	1.3*	200
	10	4/8*	12.8*	87.7*	1.3*	240
GG167	250	8/8**	>21.0**	88.6*	0.3**	163**
	50	8/8**	>21.0**	88.0*	1.5*	187*
	10	5/7*	10.5	85.2	1.5*	250
Ribavirin	100	8/8**	>21.0**	88.2*	0.3**	140**
	32	6/8*	13.0	88.0*	0.8**	163**
	10	3/8	11.0	86.4	2.2	267
Saline	-	1/16	10.9	84.5	2.4	203

Table III. Comparison of the Effect of Orally Administered^a 260, 262 and GG167 on Influenza A (H1N1) Virus Infections in Mice.

5

CC-100-01-000001-01 (10/10/17) has infections in mice.

	Compound	Dosage (mg/kg/day)	Surv/ total	% Survivors	Mean Surv. Time ^b (days)	Mean SaO ₂ ^c (%)
10	260	10	6/8**	75**	13.5**	87.6*
		1	3/5	38	11.8	86.8
		0.1	0/8	0	10.0	84.3
	262	10	8/8***	100***	>21.0**	88.1**
		1	7/8***	88***	14.0**	87.4*
		0.1	2/8	25	11.1**	85.7
15	GG167	10	5/8*	63*	12.3**	86.9
		1	2/8	25	11.7**	85.7
		0.1	0/8	0	9.8	83.5
		Saline	0	2/16	13	9.6
	20					

Footnotes for Tables I-III

^aBid x 5 beginning 4 hr pre-virus exposure.

^bAnimals dying on or before day 21.

25 ^cMean of values determined on days 3-10.

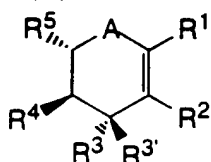
^dDetermined on day 6.

*P<0.05, **P<0.01, ***P<0.001 compared to saline-treated controls

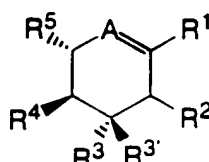
30 Surprisingly, the foregoing demonstrates that in this model the oral or
i.p. administration of GG167 was effective in practical therapeutic doses at
reducing mortality in influenza-infected mice, despite the conclusion of Ryan
et al. (*Antimicrob. Agents Chemother.*, 38(10):2270-2275) [1994]) that "it is
likely that the relatively poor in vivo activity seen with GG167 in mice
following intraperitoneal administration, despite good bioavailability, is due
35 to its rapid clearance from the plasma, permitting poor penetration into
respiratory secretions, coupled with its inability to penetrate and persist inside
cells....Similarly, the poor efficacy following oral dosing is probably a
consequence of poor oral bioavailability in addition to these other factors."
(p.2274). These observations are consistent with Von Izstein et al., WO
40 91/16320, WO 92/06691 and U.S. patent 5,360,817, which cover or are directed

specifically to GG167. These patent documents are devoid of any teaching or suggestion to administer GG167 by any other route than intranasal. However, intranasal administration is believed to be inconvenient and costly in some circumstances. It would be advantageous if more facile routes of administration could be employed for GG167 and its related compounds set forth in WO 91/16320, WO 92/06691 and U.S. patent 5,360,817.

Thus, an embodiment of this invention is a method for the treatment or prophylaxis of influenza virus infection in a host comprising administering to the host, by a route other than topically to the respiratory system, a therapeutically effective dose of an antivirally active compound having formula (X) or (Y)



(x)



(y)

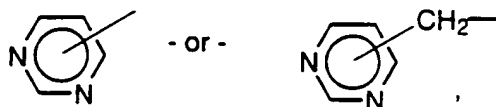
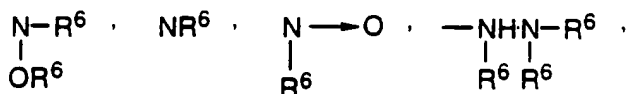
where in general formula (x), A is oxygen, carbon or sulphur, and in general formula (y), A is nitrogen or carbon;

R¹ denotes COOH, P(O)(OH)₂, NO₂, SOOH, SO₃H, tetrazol, CH₂CHO, CHO or CH(CHO)₂,

R² denotes H, OR⁶, F, Cl, Br, CN, NHR⁶, SR⁶, or CH₂X, wherein X is NHR⁶, halogen or OR⁶ and

R⁶ is hydrogen; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; an allyl group or an unsubstituted aryl group or an aryl substituted by a halogen, an OH group, an NO₂ group, an NH₂ group or a COOH group,

R³ and R^{3'} are the same or different, and each denotes hydrogen, CN, NHR⁶, N₃, SR⁶, =N-OR⁶, OR⁶, guanidino,



R^4 denotes NHR^6 , SR^6 , OR^6 , $COOR^6$, NO_2 , $C(R^6)_3$, CH_2COOR^6 , CH_2NO_2 or CH_2NHR^6 , and

R^5 denotes CH_2YR^6 , $CHYR^6CH_2YR^6$ or $CHYR^6CHYR^6CH_2YR^6$, where Y is O, S, NH or H, and successive Y moieties in an R^5 group are the same or
5 different,

and pharmaceutically acceptable salts or derivatives thereof, provided that in general formula (x)

(i) when R^3 or $R^{3'}$ is OR^6 or hydrogen, and A is oxygen or sulphur, then said compound cannot have both

10 (a) an R^2 that is hydrogen and

(b) an R^4 that is NH-acyl, and

(ii) R^6 represents a covalent bond when Y is hydrogen, and that in general formula (y),

(i) when R^3 or $R^{3'}$ is OR^6 or hydrogen, and A is nitrogen, then said
15 compound cannot have both

(a) an R^2 that is hydrogen, and

(b) an R^4 that is NH-acyl, and

(ii) R^6 represents a covalent bond when Y is hydrogen.

20 The compounds of formulas x and y are more fully described in WO 91/16320, at page 3, line 23 to page 7, line 1, WO 92/06691 and U.S. patent 5,360,817, x and y are described therein as "I" and "Ia", respectively.

For the purposes herein, administration by a route "other than topically to the respiratory tract means" does not exclude administration of
25 compound by buccal or sublingual routes, and does not exclude incidental adsorption of compound in the esophagus during oral, buccal or sublingual administration, provided however, that such as buccal, oral, sublingual or esophageal adsorption is not incidental to administration to the lungs or nasal passages by inhalers or the like. Usually, compound is administered as a
30 formed article, a slurry or a solution.

In typical embodiments of this invention, the compound is GG167, the host is an animal other than mice (such as ferrets or humans), the route of administration is oral, and the objective of treatment and prophylaxis is reduction in mortality. Optionally, a prodrug of the compound of formula (X)
35 or (Y) is employed, although as shown above it is not necessary to do so to achieve antiviral effect by oral administration. As prodrugs of GG167 and its

co-disclosed compounds, any of the esters, amides or other prodrugs described elsewhere herein for the compounds of this invention are suitable for use with the analogous groups of the compounds of formula (X) and (Y), e.g., carboxyl esters or amides.

5 The therapeutically effective dose of GG167 and its related compounds, when administered by oral or other non-nasal administration routes, will be determined by the ordinarily skilled clinician in light of the considerations set forth in connection with dosing the compounds of this invention. For the most part the principal considerations are the route of administration and the
10 host species. In general, larger doses will be required as one proceeds from intravenous to subcutaneous to oral administration routes, and in accord with conventional pharmacologic scaling principles as one proceeds to larger animals. Determination of therapeutically active doses is well within the ordinary skill in the art, but in general the doses will be substantially the same
15 as those employed for the compounds of this invention.

Example 122

Each of the reactions shown in Table 50 were preformed according to Scheme 50. The preformed reactions are indicated with a "✓". Unless
20 otherwise indicated in Table 50, steps AA, AB and AC were preformed according to Examples 92, 93 and 94, respectively, and step AD was preformed according to the combination of Examples 112 and 113.

Scheme 50

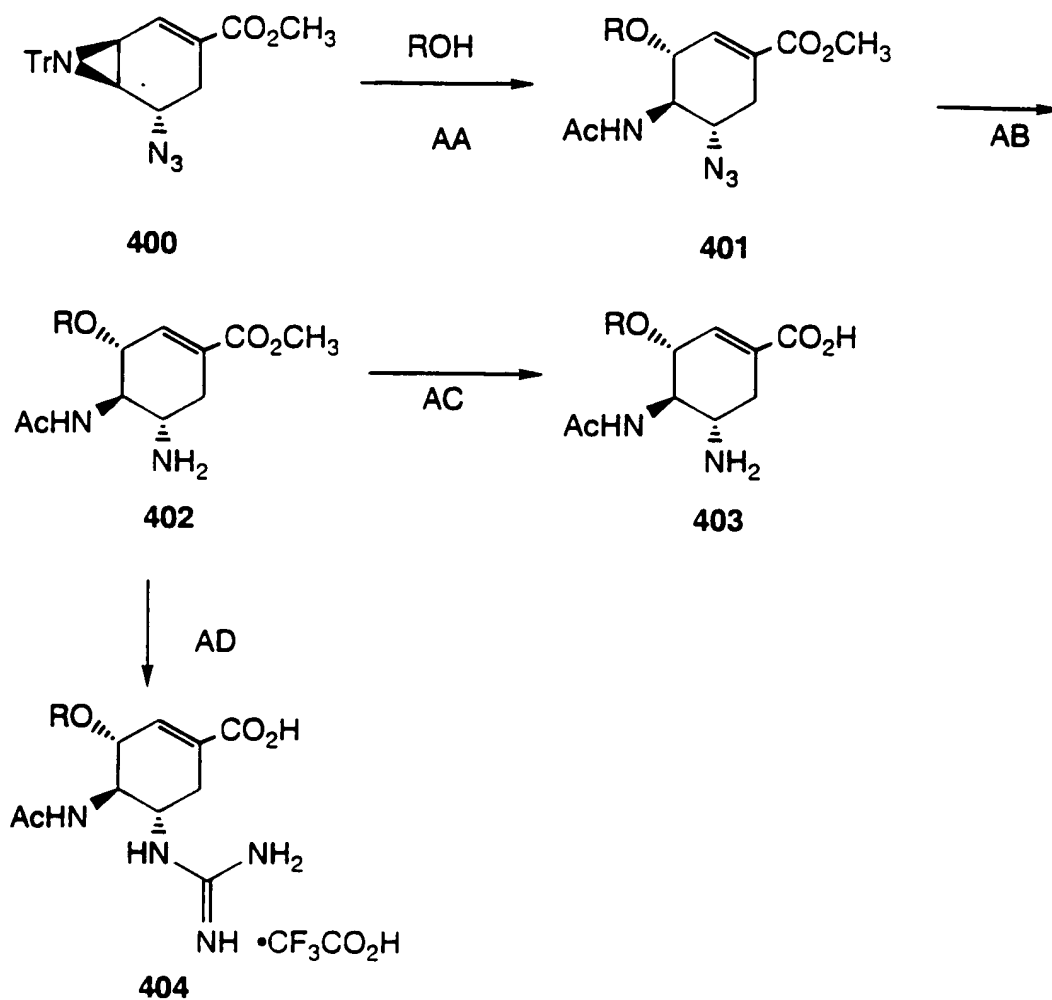


Table 50

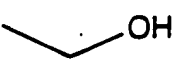
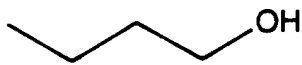
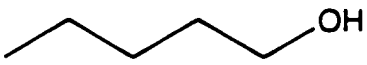
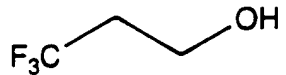
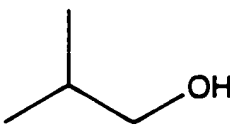
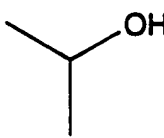
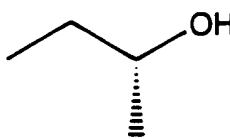

ROH	AA	AB	AC	AD
	✓	✓ a,b	✓ c	
	✓	✓ a, d	✓ c, e	✓
	✓	✓	✓	
	✓	✓	✓	
	✓	✓ d	✓ c	✓
	✓	✓ f	✓	
	✓ g	✓	✓	✓
	✓ g	✓	✓	✓

Table 50 (continued)

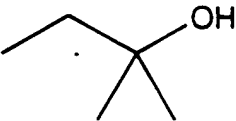
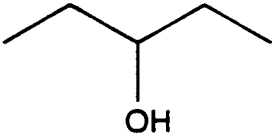
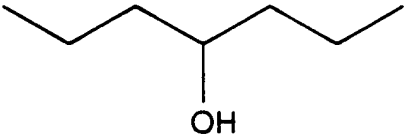
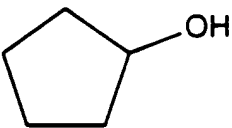
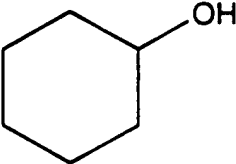
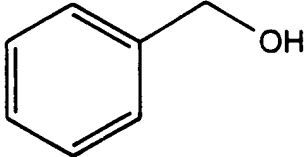
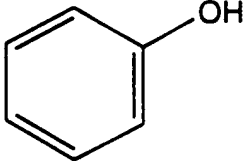
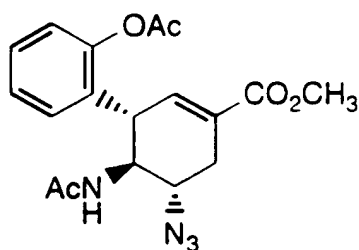
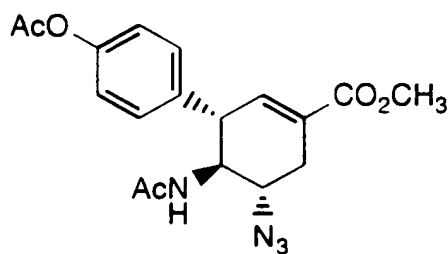
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	✓	✓	✓	✓
	✓	✓	✓	
	✓	✓ h	✓	✓
	✓	✓	✓	
	✓	✓ b, d	✓	✓
	✓ i, j	✓	✓	

Table 50 (notes)

- a) ester hydrolysis prior to azide reduction
- b) azide reduction using Ph_3P at room temperature
- c) ester hydrolysis using aqueous KOH/MeOH
- 5 d) azide reduction using polymer-support Ph_3P at room temperature
- e) isolated as the HCl salt
- f) azide reduction using Ph_3P in $\text{MeOH}/\text{THF}/\text{H}_2\text{O}$
- g) diastereomeric mixture, major diastereomer indicated
- h) azide reduction also performed with Me_3P
- 10 i) aziridine opening performed at 55°C
- j) C-alkylated products were isolated



405



406

15 Example 123

- Trifluoroacetamide 340:** To a solution of amine 228 (100 mg, 0.34 mmol) in CH_2Cl_2 (3.5 mL) at 0°C was added pyridine (41 μL , 0.51 mmol) and trifluoroacetic anhydride (TFAA) (52 μL , 0.37 mmol) and the solution was stirred for 45 min at which time additional TFAA (0.5 eq) was added. After 15 min the reaction was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and 1M HCl . The organic phase was washed with saturated NaHCO_3 , saturated NaCl , and was dried (MgSO_4), filtered, and evaporated. The residue was chromatographed on silica gel (2/1-hexane/ethyl acetate) to afford trifluoroacetamide 340 (105 mg, 78%): ^1H
- 25 NMR (CDCl_3) δ 8.64 (d, 1H, $J = 7.7$), 6.81 (s, 1H), 6.48 (d, 1H, $J = 8.2$), 4.25-4.07 (m, 3H), 3.75 (s, 3H), 3.37 (m, 1H), 2.76 (dd, 1H, $J = 4.5, 18.7$), 2.54 (m, 1H), 1.93 (s, 3H), 1.48 (m, 4H), 0.86 (m, 6H).

Example 124

N-Methyl trifluoroacetamide 341: To a solution of trifluoroacetamide **340** (90 mg, 0.23 mmol) in DMF (2 mL) at 0 °C was added sodium hydride (10 mg, 60% dispersion in mineral oil, 0.25 mmol). After 15 min at 0 °C, methyl iodide (71 µL, 1.15 mmol) was added and the reaction was stirred for 2 h at 0 °C and for 1 h at room temperature. Acetic acid (28 µL) was added and the solution was evaporated. The residue was partitioned between ethyl acetate and water. The organic phase was washed with saturated NaCl, dried (MgSO₄), filtered, and evaporated. The residue was chromatographed on silica gel (1/1-hexane/ethyl acetate) to afford N-methyl trifluoroacetamide **341** (81 mg, 87%) as a colorless glass: ¹H NMR (CDCl₃) δ 6.80 (s, 1H), 6.26 (d, 1H, *J* = 9.9), 4.67 (m, 1H), 4.32 (m, 1H), 4.11 (m, 1H), 3.78 (s, 3H), 3.32 (m, 1H), 3.07 (br s, 3H), 2.60 (m, 2H), 1.91 (s, 3H), 1.48 (m, 4H), 0.87 (m, 6H).

Example 125

N-Methyl amine 342: To a solution of N-methyl trifluoroacetamide **341** (81 mg, 0.20 mmol) in THF (3 mL) was added 1.04 N KOH (480 µL, 0.50 mmol) and the mixture was stirred at room temperature for 14 h. The reaction was acidified with IR 120 ion exchange resin to pH~4. The resin was filtered, washed with THF, and the filtrate was evaporated. The residue was dissolved in 10% TFA/water (5 mL) and was evaporated. The residue was passed through a column (1.5X2.5 cm) of C-18 reverse phase silica gel eluting with water. Product fractions were pooled and lyophilized to afford N-methyl amine **342** (46 mg, 56%) as a white solid: ¹H NMR (D₂O) δ 6.80 (s, 1H), 4.31 (br d, 1H, *J* = 8.8), 4.09 (dd, 1H, *J* = 8.9, 11.6), 3.53 (m, 2H), 2.98 (dd, 1H, *J* = 5.4, 16.9), 2.73 (s, 3H), 2.52-2.41 (m, 1H), 2.07 (s, 3H), 1.61-1.39 (m, 4H), 0.84 (m, 6H).

Example 126

Compound 346: To a solution of epoxide **345** (13.32 g, 58.4 mmol) in 8/1-MeOH/H₂O (440 mL, v/v) was added sodium azide (19.0 g, 292.0 mmol) and ammonium chloride (2.69 g, 129.3 mmol) and the mixture was refluxed for 15h. The reaction was cooled, concentrated under reduced pressure and partitioned between EtOAc and H₂O. The organic layer was washed successively with satd. bicarb, brine and dried over MgSO₄. Concentration *in vacuo* followed by flash chromatography on silica gel (30% EtOAc in hexanes)

gave 11.81 g (75%) of azido alcohol **346** as a viscous oil. ¹H NMR(300 MHz, CDCl₃) δ 6.90-6.86 (m, 1H); 4.80 (s, 2H); 4.32 (bt, 1H, J = 4.2 Hz); 4.22 (q, 2H, J = 7.2 Hz); 3.90-3.74 (overlapping m, 2H); 3.44 (s, 3H); 2.90 (d, 1H, J = 6.9 Hz); 2.94-2.82 (m, 1H); 2.35-2.21 (m, 1H); 1.30 (t, 3H, J = 7.2 Hz).

5

Example 127

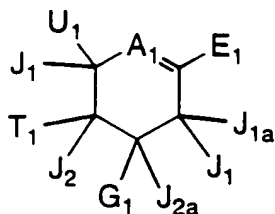
Compound 347: To a solution of ethyl ester **346** (420 mg, 1.55 mmol) in dry THF (8.0 mL) cooled to -78 °C was added DIBAL (5.1 mL of a 1.0 M solution in toluene) dropwise via syringe. The bright yellow reaction mixture was stirred at -78 °C for 1.25 h and then slowly hydrolyzed with the slow addition of MeOH (1.2 mL). Volatiles were removed under reduced pressure and the residue partitioned between EtOAc and cold dilute HCl. The organic layer was separated and the aqueous layer back extracted with EtOAc. The organic layers were combined and washed successively with satd. bicarb, brine and dried over MgSO₄. Concentration *in vacuo* followed by flash chromatography on silica gel (20% hexanes in EtOAc) gave 127 mg (36%) of the diol **347** as a colorless viscous oil. ¹H NMR(300 MHz, CDCl₃) δ 5.83-5.82 (m, 1H); 4.78 (s, 2H); 4.21 (bt, 1H, J = 4.4 Hz); 4.06 (bs, 2H); 3.85-3.65 (overlapping m, 2H); 3.43 (s, 3H); 3.18 (d, 1H, J = 8.1 Hz); 2.51 (dd, 1H, J = 5.5, 17.7 Hz); 2.07-1.90 (m, 1H); 1.92 (bs, 1H).

15
20

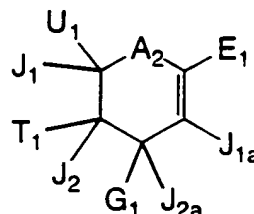
The following claims are directed to embodiments of the invention and shall be construed to cover in substantial variations thereof.

What is Claimed Is:

1. A composition comprising a compound of formula (I) or (II):



(I)



(II)

- 5 wherein

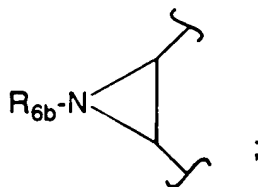
A₁ is -C(J₁)=, or -N=;

A₂ is -C(J₁)₂-, -N(J₁)-, -N(O)(J₁)-, -N(O)=, -S-, -S(O)-, -S(O)₂- or -O-;

E₁ is -(CR₁R₁)_{m1}W₁;

G₁ is N₃, -CN, -OH, -OR_{6a}, -NO₂, or -(CR₁R₁)_{m1}W₂;

- 10 T₁ is -NR₁W₃, a heterocycle, or is taken together with U₁ or G₁ to form a group having the structure



U₁ is H or -X₁W₆;

J₁ and J_{1a} are independently R₁, Br, Cl, F, I, CN, NO₂ or N₃;

- 15 J₂ and J_{2a} are independently H or R₁;

R₁ is independently H or alkyl of 1 to 12 carbon atoms;

R₂ is independently R₃ or R₄ wherein each R₄ is independently substituted with 0 to 3 R₃ groups;

- 20 R₃ is independently F, Cl, Br, I, -CN, N₃, -NO₂, -OR_{6a}, -OR₁, -N(R₁)₂, -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, -SR_{6a}, -S(O)R₁, -S(O)₂R₁, -S(O)OR₁, -S(O)OR_{6a}, -S(O)₂OR₁, -S(O)₂OR_{6a}, -C(O)OR₁, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R₁, -N(R₁)(C(O)R₁), -N(R_{6b})(C(O)R₁), -N(R₁)(C(O)OR₁), -N(R_{6b})(C(O)OR₁), -C(O)N(R₁)₂, -C(O)N(R_{6b})(R₁), -C(O)N(R_{6b})₂, -C(NR₁)(N(R₁)₂), -C(N(R_{6b}))(N(R₁)₂), -C(N(R₁))(N(R₁)(R_{6b})), -C(N(R_{6b}))(N(R₁)(R_{6b})),
- 25 -C(N(R₁))(N(R_{6b})₂), -C(N(R_{6b}))(N(R_{6b})₂), -N(R₁)C(N(R₁))(N(R₁)₂), -N(R₁)C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)₂), -N(R_{6b})C(N(R₁))(N(R₁)₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)₂), -N(R_{6b})C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)(R_{6b})),

-N(R₁)C(N(R₁))(N(R_{6b})₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)(R_{6b})),
 -N(R_{6b})C(N(R₁))(N(R_{6b})₂), -N(R₁)C(N(R_{6b}))(N(R_{6b})₂),
 -N(R_{6b})C(N(R_{6b}))(N(R_{6b})₂), =O, =S, =N(R₁) or =N(R_{6b});

R₄ is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12
 5 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R₅ is independently R₄ wherein each R₄ is substituted with 0 to 3 R₃
 groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2
 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which
 10 alkylene, alkenylene or alkynylene is substituted with 0-3 R₃ groups;

R_{6a} is independently H or an ether- or ester-forming group;

R_{6b} is independently H, a protecting group for amino or the residue of a
 carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing
 15 compound;

W₁ is a group comprising an acidic hydrogen, a protected acidic group,
 or an R_{6c} amide of the group comprising an acidic hydrogen;

W₂ is a group comprising a basic heteroatom or a protected basic
 heteroatom, or an R_{6b} amide of the basic heteroatom;

20 W₃ is W₄ or W₅;

W₄ is R₅ or -C(O)R₅, -C(O)W₅, -SO₂R₅, or -SO₂W₅;

W₅ is carbocycle or heterocycle wherein W₅ is independently
 substituted with 0 to 3 R₂ groups;

W₆ is -R₅, -W₅, -R_{5a}W₅, -C(O)OR_{6a}, -C(O)R_{6c}, -C(O)N(R_{6b})₂,
 25 -C(NR_{6b})(N(R_{6b})₂), -C(NR_{6b})(N(H)(R_{6b})), -C(N(H)(N(R_{6b})₂), -C(S)N(R_{6b})₂, or
 -C(O)R₂;

X₁ is a bond, -O-, -N(H)-, -N(W₆)-, -N(OH)-, -N(OW₆)-, -N(NH₂)-,
 -N(N(H)(W₆))-, -N(N(W₆)₂)-, -N(H)N(W₆)-, -S-, -SO-, or -SO₂-; and

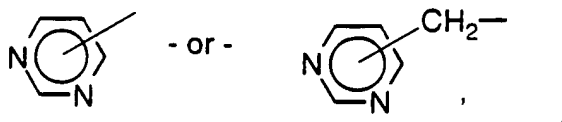
each m₁ is independently an integer from 0 to 2;

30 *provided*, however, that compounds are excluded wherein:

(a) A₁ is -CH= or -N= and A₂ is -CH₂-;

(b) E₁ is COOH, P(O)(OH)₂, SOOH, SO₃H, or tetrazol;

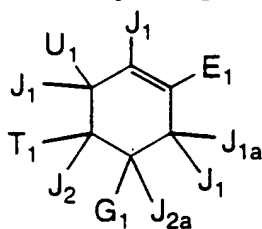
- (c) G_1 is CN, $N(H)R_{20}$, N_3 , SR_{20} , OR_{20} , guanidino, $-N(H)CN$
 $\begin{array}{c} N-R_{20} \\ | \\ OR_{20} \end{array}$, NR_{20} , $\begin{array}{c} N \rightarrow O \\ | \\ R_{20} \end{array}$, $\begin{array}{c} -NHN-R_{20} \\ | \quad | \\ R_{20} \quad R_{20} \end{array}$



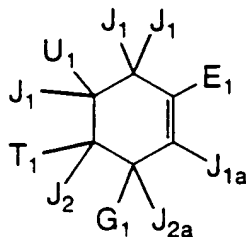
- (d) T_1 is $-NHR_{20}$;
- 5 (e) R_{20} is H; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; an allyl group or an unsubstituted aryl group or an aryl substituted by a halogen, an OH group, an NO_2 group, an NH_2 group or a
- 10 $COOH$ group;
- (f) J_1 is H and J_{1a} is H, F, Cl, Br or CN;
- (g) J_2 is H and J_{2a} is H, CN or N_3 ;
- (h) U_1 is CH_2YR_{20a} , $CHYR_{20a}CH_2YR_{20a}$ or $CHYR_{20a}CHYR_{20a}CH_2YR_{20a}$;
- 15 (i) R_{20a} is H or acyl having 1 to 4 carbon atoms;
- (j) Y is O, S, H or NH;
- (k) 0 to 2 YR_{20a} are H, and
- (l) successive Y moieties in a U_1 group are the same or different, and when Y is H then R_{20a} is a covalent bond,
- 20 and *provided* that if G_1 is N_3 then U_1 is not $-CH_2OCH_2Ph$.
 and the pharmaceutically acceptable salts and solvates thereof;

and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

2. A composition comprising a compound of formula (III) or (IV):



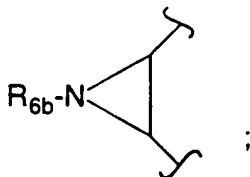
(III)



(IV)

wherein

- 5 E₁ is -(CR₁R₁)_{m1}W₁;
 G₁ is N₃, -CN, -OH, -OR_{6a}, -NO₂, or -(CR₁R₁)_{m1}W₂;
 T₁ is -NR₁W₃, a heterocycle, or is taken together with U₁ or G₁ to form
 a group having the structure



- 10 U₁ is H or -X₁W₆ and, if -X₁W₆, then U₁ is a branched chain other
 than C₂-C₃ alkyl substituted with 1 to 3 OAc groups;
 J₁ and J_{1a} are independently R₁, Br, Cl, F, I, CN, NO₂ or N₃;
 J₂ and J_{2a} are independently H or R₁;
 R₁ is independently H or alkyl of 1 to 12 carbon atoms;
 15 R₂ is independently R₃ or R₄ wherein each R₄ is independently
 substituted with 0 to 3 R₃ groups;
 R₃ is independently F, Cl, Br, I, -CN, N₃, -NO₂, -OR_{6a}, -OR₁, -N(R₁)₂,
 -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, -SR_{6a}, -S(O)R₁, -S(O)₂R₁, -S(O)OR₁, -S(O)OR_{6a},
 -S(O)₂OR₁, -S(O)₂OR_{6a}, -C(O)OR₁, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R₁,
 20 -N(R₁)(C(O)R₁), -N(R_{6b})(C(O)R₁), -N(R₁)(C(O)OR₁), -N(R_{6b})(C(O)OR₁),
 -C(O)N(R₁)₂, -C(O)N(R_{6b})(R₁), -C(O)N(R_{6b})₂, -C(NR₁)(N(R₁)₂),
 -C(N(R_{6b}))(N(R₁)₂), -C(N(R₁))(N(R₁)(R_{6b})), -C(N(R_{6b}))(N(R₁)(R_{6b})),
 -C(N(R₁))(N(R_{6b})₂), -C(N(R_{6b}))(N(R_{6b})₂), -N(R₁)C(N(R₁))(N(R₁)₂),
 -N(R₁)C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)₂),
 25 -N(R_{6b})C(N(R₁))(N(R₁)₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)₂),
 -N(R_{6b})C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)(R_{6b})),
 -N(R₁)C(N(R₁))(N(R_{6b})₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)(R_{6b})),
 -N(R_{6b})C(N(R₁))(N(R_{6b})₂), -N(R₁)C(N(R_{6b}))(N(R_{6b})₂),

$-N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2), =O, =S, =N(R_1)$ or $=N(R_{6b})$;

R_4 is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R_5 is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms which is substituted with 0-3 R_3 groups;

R_{6a} is independently H or an ether-or ester-forming group;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W_2 is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W_3 is W_4 or W_5 ;

W_4 is R_5 or $-C(O)R_5$, $-C(O)W_5$, $-SO_2R_5$, or $-SO_2W_5$;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

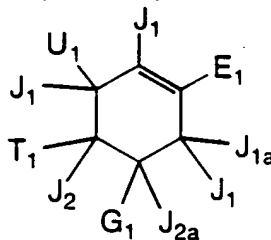
W_6 is $-R_5$, $-W_5$, $-R_{5a}W_5$, $-C(O)OR_{6a}$, $-C(O)R_{6c}$, $-C(O)N(R_{6b})_2$, $-C(NR_{6b})(N(R_{6b})_2)$, $-C(S)N(R_{6b})_2$, or $-C(O)R_2$;

X_1 is a bond, $-O-$, $-N(H)-$, $-N(W_6)-$, $-N(OH)-$, $-N(OW_6)-$, $-N(NH_2)-$, $-N(N(H)(W_6))-$, $-N(N(W_6)_2)-$, $-N(H)N(W_6)-$, $-S-$, $-SO-$, or $-SO_2-$; and

each m_1 is independently an integer from 0 to 2;

and the salts, solvates, resolved enantiomers and purified diastereomers

3. A composition comprising a compound of formula (III):



(III)

30

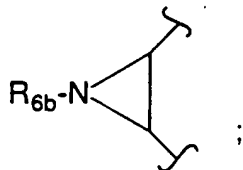
wherein

E₁ is -(CR₁R₁)_{m1}W₁;

G₁ is N₃, -CN, -OH, -OR_{6a}, -NO₂, or -(CR₁R₁)_{m1}W₂;

T₁ is -NR₁W₃, a heterocycle, or is taken together with U₁ or G₁ to form

5 a group having the structure



U₁ is H or -X₁W₆;

J₁ and J_{1a} are independently R₁, Br, Cl, F, I, CN, NO₂ or N₃;

J₂ and J_{2a} are independently H or R₁;

10 R₁ is independently H or alkyl of 1 to 12 carbon atoms;

R₂ is independently R₃ or R₄ wherein each R₄ is independently substituted with 0 to 3 R₃ groups;

R₃ is independently F, Cl, Br, I, -CN, N₃, -NO₂, -OR_{6a}, -OR₁, -N(R₁)₂,
 -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, -SR_{6a}, -S(O)R₁, -S(O)₂R₁, -S(O)OR₁, -S(O)OR_{6a},
 15 -S(O)₂OR₁, -S(O)₂OR_{6a}, -C(O)OR₁, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R₁,
 -N(R₁)(C(O)R₁), -N(R_{6b})(C(O)R₁), -N(R₁)(C(O)OR₁), -N(R_{6b})(C(O)OR₁),
 -C(O)N(R₁)₂, -C(O)N(R_{6b})(R₁), -C(O)N(R_{6b})₂, -C(NR₁)(N(R₁)₂),
 -C(N(R_{6b}))(N(R₁)₂), -C(N(R₁))(N(R₁)(R_{6b})), -C(N(R_{6b}))(N(R₁)(R_{6b})),
 -C(N(R₁))(N(R_{6b})₂), -C(N(R_{6b}))(N(R_{6b})₂), -N(R₁)C(N(R₁))(N(R₁)₂),
 20 -N(R₁)C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)₂),
 -N(R_{6b})C(N(R₁))(N(R₁)₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)₂),
 -N(R_{6b})C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)(R_{6b})),
 -N(R₁)C(N(R₁))(N(R_{6b})₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)(R_{6b})),
 -N(R_{6b})C(N(R₁))(N(R_{6b})₂), -N(R₁)C(N(R_{6b}))(N(R_{6b})₂),
 25 -N(R_{6b})C(N(R_{6b}))(N(R_{6b})₂), =O, =S, =N(R₁) or =N(R_{6b});

R₄ is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R₅ is independently R₄ wherein each R₄ is substituted with 0 to 3 R₃ groups;

30 R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms which is substituted with 0-3 R₃ groups;

R_{6a} is independently H or an ether- or ester-forming group;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

5 W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W_2 is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W_3 is W_4 or W_5 ;

10 W_4 is R_5 or $-C(O)R_5$, $-C(O)W_5$, $-SO_2R_5$, or $-SO_2W_5$;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

W_6 is $-R_5$, $-W_5$, $-R_{5a}W_5$, $-C(O)OR_{6a}$, $-C(O)R_{6c}$, $-C(O)N(R_{6b})_2$, $-C(NR_{6b})(N(R_{6b})_2)$, $-C(S)N(R_{6b})_2$, or $-C(O)R_2$;

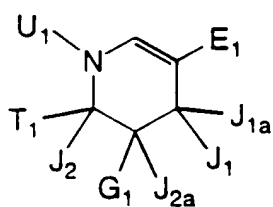
15 X_1 is $-O-$, $-N(H)-$, $-N(W_6)-$, $-N(OH)-$, $-N(OW_6)-$, $-N(NH_2)-$, $-N(N(H)(W_6))-$, $-N(N(W_6)_2)-$, $-N(H)N(W_6)-$, $-S-$, $-SO-$, or $-SO_2-$; and

each m_1 is independently an integer from 0 to 2;

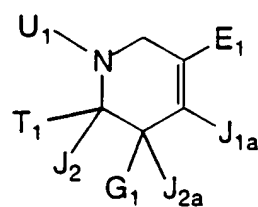
and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

20

4. A composition comprising a compound of formula (VII) or (VIII):



(VII)



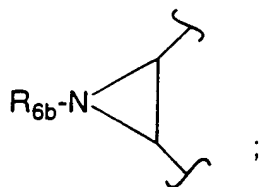
(VIII)

wherein

25 E_1 is $-(CR_1R_1)_{m_1}W_1$;

G_1 is N_3 , $-CN$, $-OH$, $-OR_{6a}$, $-NO_2$, or $-(CR_1R_1)_{m_1}W_2$;

T_1 is $-NR_1W_3$, a heterocycle, or is taken together with G_1 to form a group having the structure



U₁ is -X₁W₆;

J₁ and J_{1a} are independently R₁, Br, Cl, F, I, CN, NO₂ or N₃;

J₂ and J_{2a} are independently H or R₁;

5 R₁ is independently H or alkyl of 1 to 12 carbon atoms;

R₂ is independently R₃ or R₄ wherein each R₄ is independently substituted with 0 to 3 R₃ groups;

R₃ is independently F, Cl, Br, I, -CN, N₃, -NO₂, -OR_{6a}, -OR₁, -N(R₁)₂,
 -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, -SR_{6a}, -S(O)R₁, -S(O)₂R₁, -S(O)OR₁, -S(O)OR_{6a},
 10 -S(O)₂OR₁, -S(O)₂OR_{6a}, -C(O)OR₁, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R₁,
 -N(R₁)(C(O)R₁), -N(R_{6b})(C(O)R₁), -N(R₁)(C(O)OR₁), -N(R_{6b})(C(O)OR₁),
 -C(O)N(R₁)₂, -C(O)N(R_{6b})(R₁), -C(O)N(R_{6b})₂, -C(NR₁)(N(R₁)₂),
 -C(N(R_{6b}))(N(R₁)₂), -C(N(R₁))(N(R₁)(R_{6b})), -C(N(R_{6b}))(N(R₁)(R_{6b})),
 -C(N(R₁))(N(R_{6b})₂), -C(N(R_{6b}))(N(R_{6b})₂), -N(R₁)C(N(R₁))(N(R₁)₂),
 15 -N(R₁)C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)₂),
 -N(R_{6b})C(N(R₁))(N(R₁)₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)₂),
 -N(R_{6b})C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)(R_{6b})),
 -N(R₁)C(N(R₁))(N(R_{6b})₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)(R_{6b})),
 -N(R_{6b})C(N(R₁))(N(R_{6b})₂), -N(R₁)C(N(R_{6b}))(N(R_{6b})₂),
 20 -N(R_{6b})C(N(R_{6b}))(N(R_{6b})₂), =O, =S, =N(R₁) or =N(R_{6b});

R₄ is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R₅ is independently R₄ wherein each R₄ is substituted with 0 to 3 R₃ groups;

25 R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R₃ groups;

R_{6a} is independently H or an ether- or ester-forming group;

30 R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W₁ is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W₂ is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W₃ is W₄ or W₅;

W₄ is R₅ or -C(O)R₅, -C(O)W₅, -SO₂R₅, or -SO₂W₅;

W₅ is carbocycle or heterocycle wherein W₅ is independently substituted with 0 to 3 R₂ groups;

W₆ is -R₅, -W₅, -R_{5a}W₅, -C(O)OR_{6a}, -C(O)R_{6c}, -C(O)N(R_{6b})₂, -C(NR_{6b})(N(R_{6b})₂), -C(NR_{6b})(N(H)(R_{6b})), -C(N(H)(N(R_{6b})₂), -C(S)N(R_{6b})₂, or -C(O)R₂;

X₁ is a bond, -O-, -N(H)-, -N(W₆)-, -S-, -SO-, or -SO₂-; and

each m₁ is independently an integer from 0 to 2;

provided, however, that compounds are excluded wherein U₁ is H or -CH₂CH(OH)CH₂(OH);

and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

5. The composition of Claim 1 further provided that if G₁ is N₃ then U₁ is not C₁-C₃ alkyl substituted with protected hydroxyl.

6. The composition of Claims 1, 2, 3, or 4 wherein R_{6a} is a protecting group for hydroxyl or thio.

7. The composition of Claims 1, 2 or 4 wherein X₁ is a bond and W₆ is neither C₁-C₄ normal alkyl nor C₁-C₄ normal alkyl substituted with 1 to 3 OH, SH or NH₂.

8. The composition of Claims 1, 2 or 4 wherein X₁ is a bond and W₆ is neither C₁-C₃ normal alkyl nor C₁-C₃ normal alkyl substituted with 1 to 3 OH, SH or NH₂.

9. The composition of Claims 1, 2 or 4 wherein X₁ is a bond and W₆ is neither C₁-C₄ normal alkyl nor C₁-C₄ normal alkyl substituted with 1 to 3 OH, OR_{6a}, SH or NH₂, wherein this R_{6a} is a protecting group.

10. The composition of Claims 1, 2 or 4 wherein X_1 is a bond and W_6 is neither C_1 - C_3 normal alkyl nor C_1 - C_3 normal alkyl substituted with 1 to 3 OH, OR_{6a} , SH or NH_2 , wherein this R_{6a} is a protecting group.
- 5 11. The composition of Claim 1 wherein the proviso further excludes compounds wherein G_1 is $(alk)_{m_4}NR^{6b}R^{7b}$;
 alk is unsubstituted or substituted methylene;
 m_4 is 0 or 1;
 10 R^{6b} is hydrogen, C_1 -6alkyl, aryl, araalkyl, amidine, $NR^{7b}R^{8b}$, or an unsaturated or saturated ring containing one or more heteroatoms;
 R^{7b} is hydrogen, C_1 -6alkyl, or allyl, or $NR^{6b}R^{7b}$ forms an optionally substituted 5 or 6 membered ring optionally containing one or more additional heteroatoms; and
 15 R^{8b} is hydrogen or C_1 -6alkyl.
12. The composition of Claim 11 wherein the proviso further excludes compounds wherein G_1 is $NR^{6b}R^{7b}$.
- 20 13. The composition of Claims 1, 2, 3 or 4 wherein W_6 is C_1 - C_3 alkyl substituted with 1 to 3 OR_{6a} or SR_{6a} , which OR_{6a} or SR_{6a} groups are stable to hydrolysis in gastrointestinal fluid.
14. The composition of Claims 1, 2, 3 or 4 wherein if W_6 is substituted with
 25 R_3 and R_3 is substituted with OR_{6a} then this R_{6a} is not acetyl.
15. The composition of Claims 1, 2, 3 or 4 wherein W_6 is
 $-(CH_2)_{m_1}CH((CH_2)_{m_3}R_3)_2$, $-(CH_2)_{m_1}C((CH_2)_{m_3}R_3)_3$;
 $-(CH_2)_{m_1}CH((CH_2)_{m_3}R_{5a}W_5)_2$; $-(CH_2)_{m_1}CH((CH_2)_{m_3}R_3)((CH_2)_{m_3}R_{5a}W_5)$;
 30 $-(CH_2)_{m_1}C((CH_2)_{m_3}R_3)_2(CH_2)_{m_3}R_{5a}W_5$, $(CH_2)_{m_1}C((CH_2)_{m_3}R_{5a}W_5)_3$ or
 $-(CH_2)_{m_1}C((CH_2)_{m_3}R_3)((CH_2)_{m_3}R_{5a}W_5)_2$ and m_3 is an integer from 1 to 3.
16. The composition of Claims 1, 2 or 4 wherein X_1 is a bond and W_6 is $-R_5$, $-W_5$ or $-R_{5a}W_5$.
- 35 17. The composition of Claims 1, 2 or 4 wherein X_1 is a bond and W_6 is R_5 .

18. The composition of Claim 17 wherein said R₅ is R₄ substituted with 0 to 3 -OR₁.
19. The composition of Claim 17 wherein said R₅ is R₄ substituted with 0 to 3 -NO₂ or N₃ groups.
20. The composition of Claim 18 wherein said -OR₁ is present and at least one of said R₁ is C₄-C₁₂.
21. The composition of Claims 1, 2, 3 or 4 wherein U₁ is -N(R₅)₂, -N(H)(CH(R_{5b})₂), -N(H)(CH₂CH(R_{5c})₂), -N(OR₅)(R₅), -N(N(H)(R₅))(R₅), -N(H)(N(R₅)₂), -N(R₅)(C(O)R₅), -C(O)N(R₅)₂, -C(S)N(R₅)₂, -OR_{5d}, -OCH(R_{5b})₂, -OCH₂CH(R_{5c})₂, -SR_{5d}, -SCH(R_{5b})₂, -SCH₂CH(R_{5c})₂, -S(O)R_{5d}, -S(O)CH(R_{5b})₂, -S(O)CH₂CH(R_{5c})₂, -S(O)₂R_{5d}, -S(O)₂CH(R_{5b})₂, -S(O)₂CH₂CH(R_{5c})₂, -C(N(R₅))(N(H)(R₅)), -C(O)R_{5d}, -C(O)CH(R_{5b})₂ or -C(O)CH₂CH(R_{5c})₂; and
 wherein:
 hydrogen of said U₁ -CH₂- or -CH- moieties optionally is substituted with -OR₁, -SR₁, NO₂, N₃, F, -CN, Cl or Br;
 R_{5b} is independently alkyl of 1 to 11 carbon atoms, alkenyl of 2 to 11 carbon atoms or alkynyl of 2 to 11 carbon atoms any one of which alkyl, alkenyl or alkynyl groups is substituted with 0 - 3 R₃ groups;
 R_{5c} is independently alkyl of 1 to 10 carbon atoms, alkenyl of 2 to 10 carbon atoms or alkynyl of 2 to 10 carbon atoms any one of which alkyl, alkenyl or alkynyl groups is substituted with 0 - 3 R₃ groups;
 R_{5d} is a branched R₅ group; and
 wherein if R₅, R_{5b}, R_{5c} or R_{5d} is substituted with 1 - 3 R₃ groups then R₃ is -OR₁, -SR₁, NO₂, N₃, F, -CN, Cl or Br.
22. The composition of Claims 1, 2, 3 or 4 wherein W₆ is a branched chain R₅ group.
23. The composition of Claim 22 wherein said R₅ is a branched R₄ group.
24. The composition of Claims 1, 2, 3 or 4 wherein W₆ is R_{5e} wherein R_{5e} is normal or secondary alkyl of 1 to 12 carbon atoms substituted with 1-3 OR_{1a} or SR_{1a} wherein R_{1a} is C₁-C₄ alkyl.

25. The composition of Claim 22 provided that when W₆ is R₅ substituted with 1 to 3 R₃ groups and at least one R₃ group is OH, COOH, NH₂, C(O)H, C(O)NH₂, S(O)₂OH, S(O)OH, N(H)(C(O)OH), C(N(H))NH₂,

5 N(H)(C(NH₂)N(H)), =O, or =N(H), then said R₅ is substituted with a single OH, COOH, NH₂, C(O)H, C(O)NH₂, S(O)₂OH, S(O)OH, N(H)(C(O)OH), C(N(H))NH₂, N(H)(C(NH₂)N(H)), =O, or =NH group.

10 26. The composition of Claim 22 wherein said R₅ is alkyl of 4 to 8 carbon atoms substituted with 0 to 3 R₃ groups.

27. The composition of Claim 22 wherein said R₅ is substituted with 0 to 2 R₃ groups.

15 28. The composition of Claim 27 wherein said R₅ is substituted with 1 to 2 R₃ groups and at least one said R₃ group is OH, COOH, NH₂, C(O)H, C(O)NH₂, S(O)₂OH, S(O)OH, N(H)(C(O)OH), C(N(H))NH₂, N(H)C((NH₂)N(H)), =O, or =NH.

20 29. The composition of Claim 28 wherein a OH, COOH, NH₂, C(O)H, C(O)NH₂, S(O)₂OH, S(O)OH, N(H)(C(O)OH), C(N(H))NH₂, N(H)C((NH₂)N(H)), =O, or =NH group substitutes a terminal carbon distal to X₁.

25 30. The composition of Claim 28 wherein a OH, COOH, NH₂, C(O)H, C(O)NH₂, S(O)₂OH, S(O)OH, N(H)(C(O)OH), C(N(H))NH₂, N(H)C((NH₂)N(H)), =O, or =NH group substitutes a carbon atom which is not a terminal carbon atom distal to X₁.

30 31. The composition of Claims 1, 2, 3 or 4 wherein W₆ is R₄ having 1 to 7 carbon atoms.

35 32. The composition of Claims 1, 2, 3 or 4 wherein said U₁ is not C₁-C₃ alkyl substituted with OH or OH protected with an aralkyl, acyl, a silicon protecting group or a tetrahydropyran.

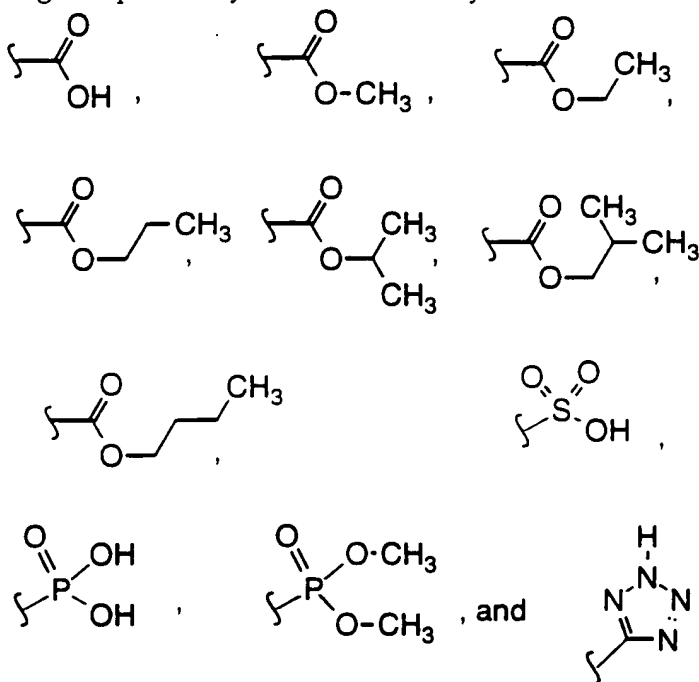
33. The composition of Claim 32 wherein the aralkyl protecting group is benzyl, triphenylmethyl or diphenylmethyl; the acyl group is acetyl; and the silicon protecting group is trimethylsilyl.
- 5 34. The composition of Claims 1, 2, 3 or 4 wherein X_1 is -O-, -N(H)-, -N(R₅)-, -N(OH)-, -N(OR₅)-, -S(O)- or -S-.
35. The composition of Claim 1 having formula (I).
- 10 36. The composition of Claim 35 wherein A_1 is C(J₁) and X_1 is -O-.
37. The composition of Claim 35 wherein A_1 is C(J₁) and X_1 is -NH-.
38. The composition of Claim 35 wherein A_1 is C(J₁) and X_1 is -N(R₅)-.
- 15 39. The composition of Claim 35 wherein A_1 is C(J₁) and X_1 is -N(OH)-.
40. The composition of Claim 35 wherein A_1 is C(J₁) and X_1 is -N(OR₅)-.
- 20 41. The composition of Claim 35 wherein A_1 is C(J₁) and X_1 is -S-.
42. The composition of Claim 35 wherein A_1 is C(J₁) and X_1 is -SO-.
43. The composition of Claim 35 wherein A_1 is -N= and X_1 is -O-.
- 25 44. The composition of Claim 35 wherein A_1 is -N= and X_1 is -NH-.
45. The composition of Claim 35 wherein A_1 is -N= and X_1 is -N(R₅)-.
- 30 46. The composition of Claim 35 wherein A_1 is -N= and X_1 is -N(OH)-.
47. The composition of Claim 35 wherein A_1 is -N= and X_1 is -N(OR₅)-.
48. The composition of Claim 35 wherein A_1 is -N= and X_1 is -S-.
- 35 49. The composition of Claim 35 wherein A_1 is -N= and X_1 is -SO-.

50. The composition of Claim 1 having formula (II).
51. The composition of Claim 50 wherein A₂ is C(J₁)₂ and X₁ is -O-.
52. The composition of Claim 50 wherein A₂ is C(J₁)₂ and X₁ is -NH-.
53. The composition of Claim 50 wherein A₂ is C(J₁)₂ and X₁ is -N(R₅)-.
54. The composition of Claim 50 wherein A₂ is C(J₁)₂ and X₁ is -N(OH)-.
55. The composition of Claim 50 wherein A₂ is C(J₁)₂ and X₁ is -N(OR₅)-.
56. The composition of Claim 50 wherein A₂ is C(J₁)₂ and X₁ is -S-.
57. The composition of Claim 50 wherein A₂ is C(J₁)₂ and X₁ is -SO-.
58. The composition of Claim 50 wherein A₂ is N(J₁) and X₁ is -O-.
59. The composition of Claim 50 wherein A₂ is N(J₁) and X₁ is -NH-.
60. The composition of Claim 50 wherein A₂ is N(J₁) and X₁ is -N(R₅)-.
61. The composition of Claim 50 wherein A₂ is N(J₁) and X₁ is -N(OH)-.
62. The composition of Claim 50 wherein A₂ is N(J₁) and X₁ is -N(OR₅)-.
63. The composition of Claim 50 wherein A₂ is N(J₁) and X₁ is -S-.
64. The composition of Claim 50 wherein A₂ is N(J₁) and X₁ is -SO-.
65. The composition of Claim 50 wherein A₂ and X₁ are -O-.
66. The composition of Claim 50 wherein A₂ is -O- and X₁ is -NH-.
67. The composition of Claim 50 wherein A₂ is -O- and X₁ is -N(R₅)-.

68. The composition of Claim 50 wherein A₂ is -O- and X₁ is -N(OH)-.
69. The composition of Claim 50 wherein A₂ is -O- and X₁ is -N(OR₅)-.
5
70. The composition of Claim 50 wherein A₂ is -O- and X₁ is -S-.
71. The composition of Claim 50 wherein A₂ is -O- and X₁ is -SO-.
- 10 72. The composition of Claim 50 wherein A₂ is -N(O)(J₁).
73. The composition of Claim 50 wherein A₂ is -N(O)-.
74. The composition of Claim 50 wherein A₂ is -S-.
- 15 75. The composition of Claim 50 wherein A₂ is -SO-.
76. The composition of Claim 50 wherein A₂ is -SO₂-.
- 20 77. The composition of any one of Claims 1, 2, 3 or 4 wherein X₁ is -O- or -N(H)-.
78. The composition of any one of Claims 1, 2, 3 or 4 wherein X₁ is -N(OR₅)- or -N(R₅)- and said R₅ is R₄ of 1 to 5 carbon atoms.
- 25 79. The composition of Claims 1, 2, 3 or 4 wherein G₁ is -NHR₁, -N(R_{6b})(R₁), -N(R_{6b})₂, -N(H)(R₅), -N(R_{6b})(R₅), -N(R₅)₂-C(NH)(NH₂), -N(R₁)C(NR₁)(NR₁R₃), -NHC(NH)(NHR₃), -NHC(NH)(NHR₁), -NHC(NH)NH₂, -CH(CH₂NHR₁)(CH₂OH),
30 -CH(CH₂NHR₁)(CH₂NHR₁), -CH(NHR₁)-(CR₁R₁)_{m2}-CH(NHR₁)R₁, -CH(OH)-(CR₁R₁)_{m2}-CH(NHR₁)R₁, or -CH(NHR₁)-(CR₁R₁)_{m2}-CH(OH)R₁, - (CR₁R₁)_{m2}-S-C(NH)NH₂, -N=C(NHR₁)(R₃) or -N=C(NHR₁)(R₁); and m₂ is independently an integer from 0 to 1.
- 35 80. The composition of Claims 1, 2, 3 or 4 wherein -C(O)R₂ of W₆ is -C(O)R₄ and X₁ is a bond, N(H)-, -N(R₅)-, -N(OH)-, or -N(OR₅)-.

81. The composition of Claims 1, 2, 3 or 4 wherein W_1 is $-\text{CO}_2\text{R}_1$.

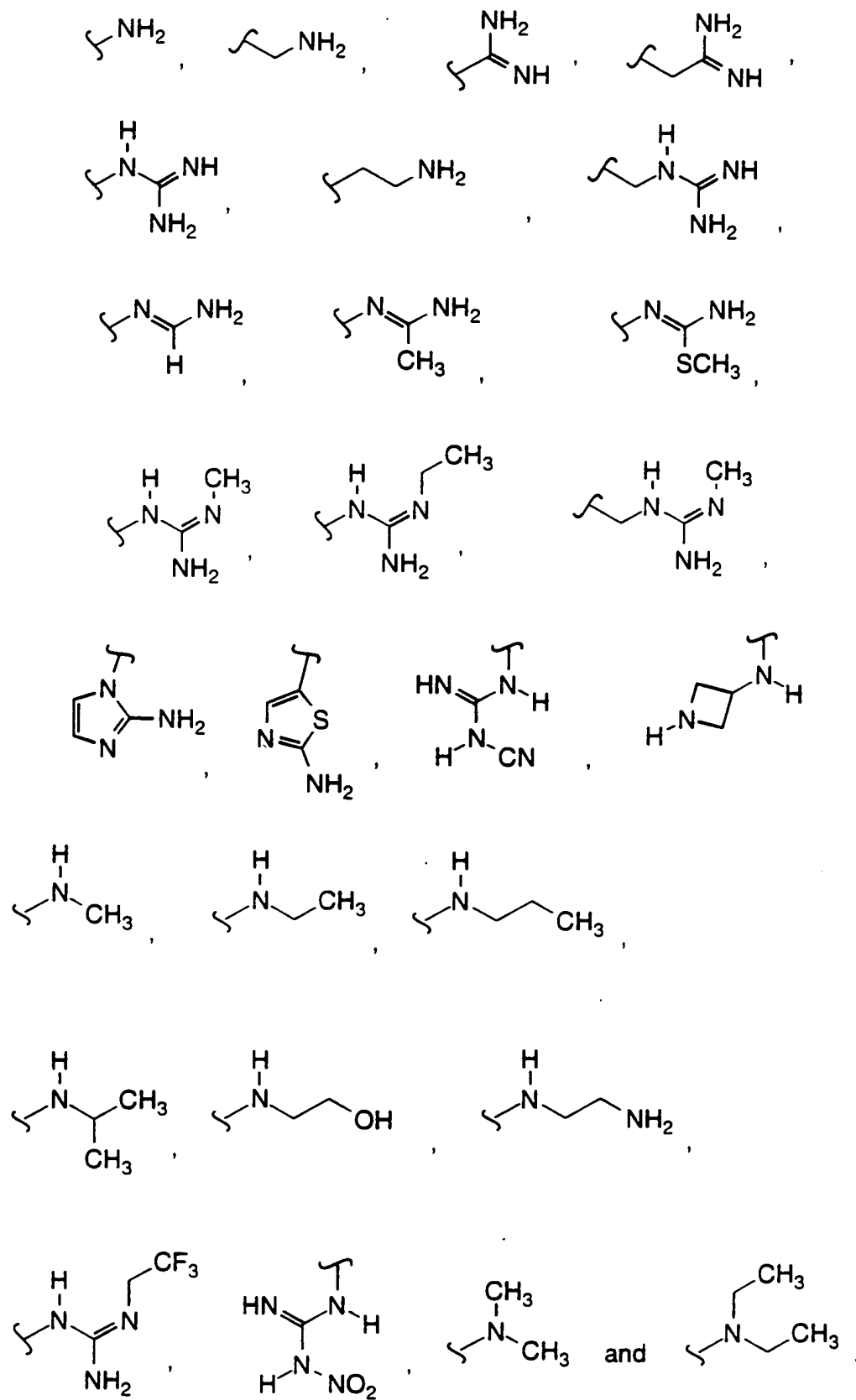
82. The composition of Claims 1, 2, 3 or 4 wherein E_1 is selected from the group consisting of: phenethyl ester of carboxyl,



83. The composition of Claims 1, 2, 3 or 4 wherein G_1 is amino, amidino or guanidino, or amino, amidino or guanidino substituted with $\text{C}_1 - \text{C}_6$ alkyl.

84. The composition of Claims 1, 2, 3 or 4 wherein W_2 is $-\text{NHR}_1$, $-\text{N}(\text{R}_{6b})(\text{R}_1)$, $-\text{N}(\text{R}_{6b})_2$, $-\text{NH}(\text{R}_5)$, $-\text{N}(\text{R}_{6b})(\text{R}_5)$, $-\text{N}(\text{R}_5)_2$, $-\text{C}(\text{NH})(\text{NH}_2)$, $-\text{NR}_1\text{C}(\text{NR}_1)(\text{NR}_1\text{R}_3)$, $-\text{NHC}(\text{NH})(\text{NHR}_3)$, $-\text{NHC}(\text{NH})(\text{NHR}_1)$, $-\text{NHC}(\text{NH})(\text{NH}_2)$, $-\text{CH}(\text{CH}_2\text{NHR}_1)(\text{CH}_2\text{OH})$, $-\text{CH}(\text{CH}_2\text{NHR}_1)(\text{CH}_2\text{NHR}_1)$, $-\text{CH}(\text{NHR}_1)-(\text{CR}_1\text{R}_1)_{m2}\text{CH}(\text{NHR}_1)\text{R}_1$, $-\text{CH}(\text{OH})(\text{CR}_1\text{R}_1)_{m2}\text{CH}(\text{NHR}_1)\text{R}_1$, or $-\text{CH}(\text{NHR}_1)(\text{CR}_1\text{R}_1)_{m2}\text{CH}(\text{OH})\text{R}_1$, $-(\text{CR}_1\text{R}_1)_{m2}\text{SC}(\text{NH})\text{NH}_2$, $-\text{N}=\text{C}(\text{NHR}_1)(\text{R}_3)$ or $-\text{N}=\text{C}(\text{NHR}_1)(\text{R}_1)$; and m_2 is independently an integer from 0 to 1.

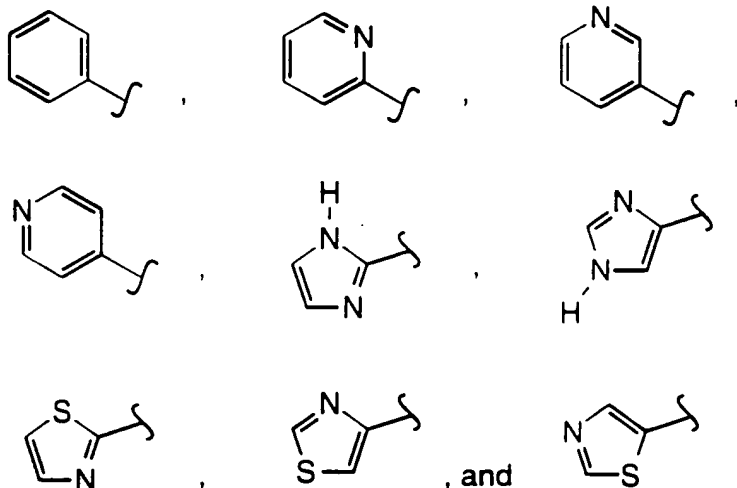
85. The composition of Claims 1, 2, 3 or 4 wherein G_1 is selected from the group consisting of: C_1 - C_6 monoalkylamine,



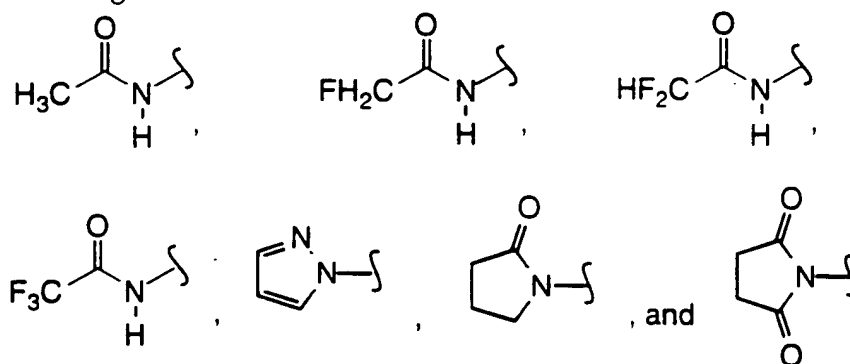
86. The composition of Claims 1, 2, 3 or 4 wherein W₃ is -C(O)-R₅.

87. The composition of Claims 1, 2, 3 or 4 wherein the R₅ of group U₁ is an alkyl of 1 to 6 carbon atoms substituted with 0 to 3 F, Br, Cl, N₃, NO₂ or CN.

88. The composition of Claims 1, 2, 3 or 4 wherein W₅ is selected from the group consisting of:



89. The composition of Claims 1, 2, 3 or 4 wherein T₁ is selected from the group consisting of:



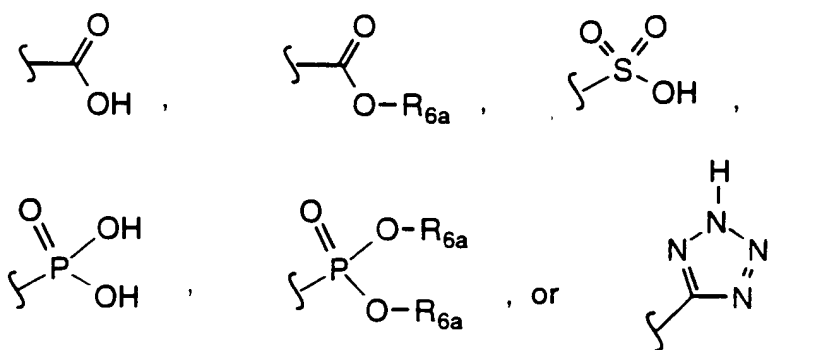
90. The composition of Claims 1, 2, 3 or 4 wherein J₁ is H, C₁-C₂ alkyl or F.

91. The composition of Claims 1, 2, 3 or 4 wherein J_{1a} is H.

92. The composition of Claims 1, 2, 3 or 4 wherein J_{2a} is H or C₁-C₂ alkyl.

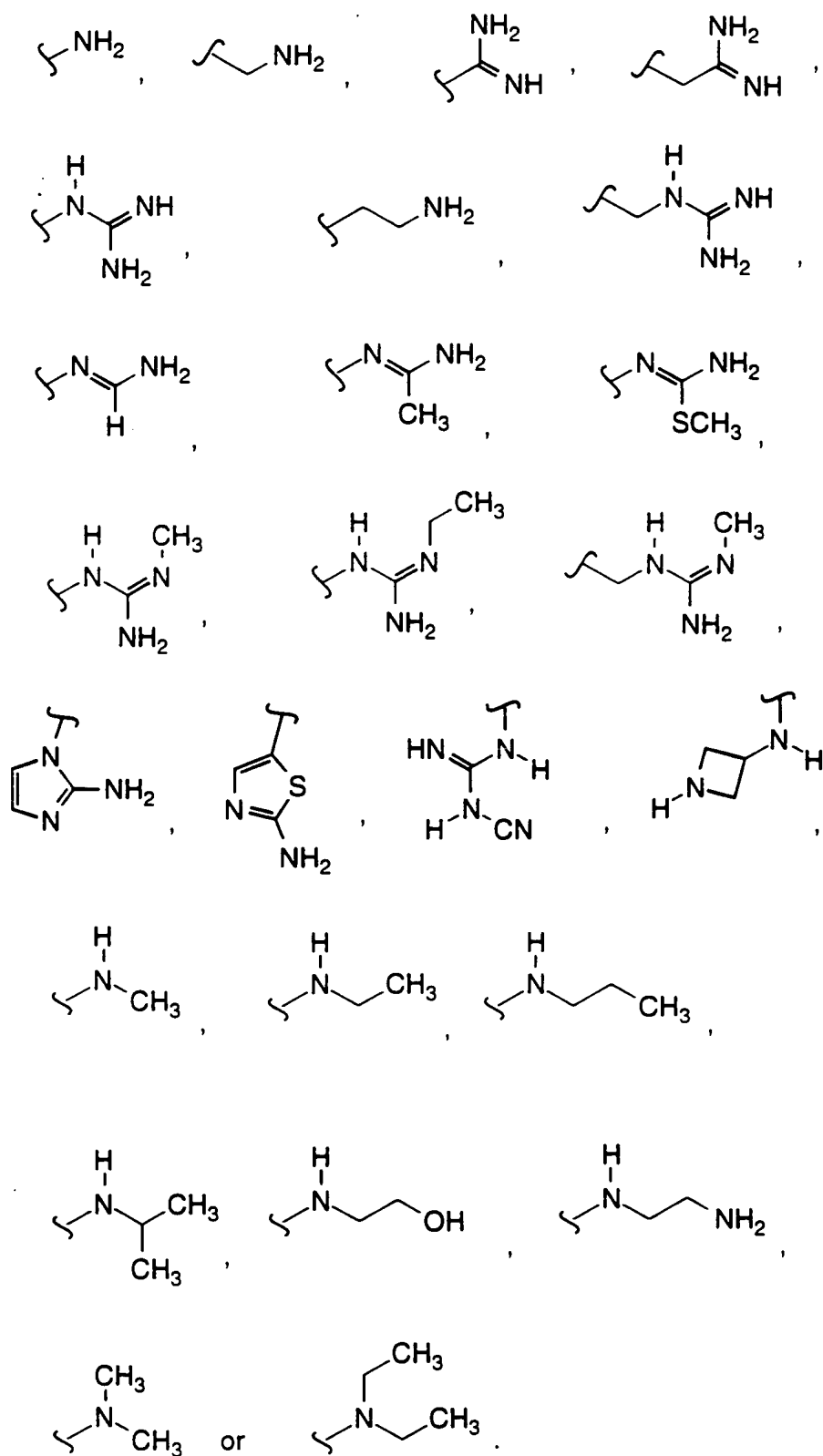
93. The composition of Claims 1, 2, 3 or 4 wherein J_{2a} is H.

94. The composition of Claims 1, 2, 3 or 4 wherein W_6 is secondary or tertiary alkyl containing 4 to 12 carbon atoms which is unsubstituted or substituted with NO_2 , N_3 , F, Br, Cl, OR_1 or SR_1 .
- 5 95. The composition of Claim 83 which is substituted with nitro, azido or F.
96. The composition of Claims 1, 2, 3 or 4 wherein W_6 is $-(CH_2)_{m1}CH(R_1)_aW_7$ wherein W_7 is an alkyl of 1 to 4 carbon atoms
 10 substituted with 0 to 3 R_3 , a is 0 or 1, and when a is 0 then W_7 is joined to CH by a double bond.
97. The composition of Claim 96 wherein U_1 is $-O-CH_2CH(R_1)W_7$.
- 15 98. The composition of Claim 96 wherein W_7 is $-CH_2OR_1$ and R_1 is C_4-C_{12} alkyl.
99. The composition of Claims 1, 2, 3 or 4 wherein U_1 is $(CH_3CH_2)_2CHO-$, $(CH_3CH_2)(CH_3)CHO-$, $(CH_3)_2CHO-$, $(CH_3)_2CHCH_2O-$, $CH_3(CH_2)_4O-$,
 20 $CH_3(CH_2)_3O-$, $CH_3(CH_2)_2O-$, $(CH_3CH_2)(CH_3)_2CO-$, $(CH_3CH_2)(CH_3CH_2)HCO-$, $(CH_3CH_2CH_2)(CH_3CH_2)HCO-$, $(CH_3CH_2CH_2)(CH_3CH_2CH_2)HCO-$, cyclohexyl-O- or cyclopentyl-O-.
100. The composition of Claims 1, 2, 3 or 4 wherein:
 25 E_1 is $-COOR_5$,



G_1 is $-N(R_5)_2$, $-NH(R_5)_2$,

30



and U₁ is an O-alkyl of 1 to 12 carbon atoms, O-alkenyl of 2 to 12 carbon atoms, or O-alkynyl of 2 to 12 carbon atoms and U₁ is substituted with 0 to 3 groups selected from the group consisting of F, Cl, Br, I, -CN, NO₂, N₃, -OR_{6a}, -NR_{6b}R_{6b}, -SR_{6a}, -O-C(O)R_{6a}, or -NR_{6b}-C(O)R_{6a}.

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101. The composition of Claim 100 wherein U₁ is selected from the group consisting of (CH₃CH₂)₂CHO-, (CH₃CH₂)(CH₃)CHO-, (CH₃)₂CHO-, (CH₃)₂CHCH₂O-, CH₃(CH₂)₄O-, CH₃(CH₂)₃O-, CH₃(CH₂)₂O-, (CH₃CH₂)(CH₃)₂CO-, (CH₃CH₂)(CH₃CH₂)HCO-,
 10 (CH₃CH₂CH₂)(CH₃CH₂)HCO-, (CH₃CH₂CH₂)(CH₃CH₂CH₂)HCO-, cyclohexyl-O-, and cyclopentyl-O-.

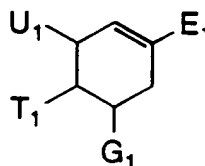
102. The composition of Claims 1, 2, 3 or 4 wherein E₁ is -COOH, or a carboxyl ester or carboxylamide that is hydrolyzable *in vivo*. to -COOH.

15

103. The composition of Claims 1, 2, 3 or 4 further comprising a pharmaceutically-acceptable carrier.

104. A composition comprising a compound of the formula:

20



wherein:

- E₁ is -CO₂H, -CO₂R₅, -CO₂R_{5a}W₅ or -CO₂W₅;
 G₁ is -N(R₁₁)₂, -N(R₁₁)C(N(R₁₁))(N(R₁₁)₂), or -C(R₁₁)₂-N(R₁₁)₂;
 25 T₁ is -NH(C(O)CH₃), -NH(C(O)CH₂F), -NH(C(O)CHF₂), or -NH(C(O)CF₃);
 U₁ is -OR₄, -SR₄, NHR₄ or N(R₄)₂;
 R₄ is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms; and
 30 R₅ is independently R₄ wherein each R₄ is substituted with 0 to 3 R₃ groups;
 R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R₃ groups

W₅ is carbocycle or heterocycle wherein W₅ is independently substituted with 0 to 3 R₂ groups; and

R₁₁ is independently H or R₅.

5 105. The composition of Claim 104 wherein:

G₁ is -NH₂, -N(H)C(N(H))(NH₂), -NHCH₃, -NHCH₂CH₃,
-N(CH₃)₂, -N(CH₂CH₃)₂, -N(CH₃)(CH₂CH₃), -NHCH₂CH₂OH,
-NHCH₂CH₂NH₂, or -CH₂-NH₂;

10 T₁ is -N(H)(C(O)CH₃), -N(H)(C(O)CH₂F), -N(H)(C(O)CHF₂), or
-N(H)(C(O)CF₃); and

R₄ is -OR₄, -SR₄ or NHR₄ is branched chain.

15 106. The composition of Claim 104 wherein R₄ is alkyl of 1 to 12 carbon atoms, and R₁₁ is R₄.

107. The composition of Claim 104 wherein R₄ is alkyl of 1 to 8 carbon atoms, or alkenyl or alkynyl of 2 to 8 carbon atoms, and R₁₁ is R₄.

20 108. The composition of Claim 104 wherein R₄ is alkyl of 1 to 6 carbon atoms, or alkenyl or alkynyl of 2 to 6 carbon atoms, and R₁₁ is R₄.

109. The composition of Claim 104 wherein R₄ is alkyl of 1 to 6 carbon atoms, and R₁₁ is R₄.

25 110. The composition of Claim 104 wherein R₄ is alkyl of 1 to 6 carbon atoms and each R₁₁ is H.

30 111. The composition of Claim 104 wherein E₁ is C(O)OCH₂CH₃; G₁ is NH₂, NHCH₃ or NHCH₂CH₃; T₁ is NH(C(O)CH₃); and U₁ is OCH(CH₂CH₃)₂.

112. A compound named in Table 6.

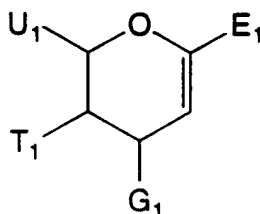
35 113. A method of inhibiting the activity of neuraminidase comprising the step of contacting a sample suspected of containing neuraminidase with the composition of Claims 1, 2, 3 or 4.

114. The method of Claim 113 wherein the neuraminidase is influenza neuraminidase *in vivo*.

115. A method for the treatment or prophylaxis of influenza infection in a host comprising administering to the host a therapeutically effective amount of a compound of Claims 1, 2, 3 or 4.

5

116. A method for the treatment or prophylaxis of virus infection in a host comprising administering to the host a therapeutically effective amount of a compound having the formula:



10

wherein:

T_1 is $-NHC(O)CH_3$, $-NHC(O)CH_2F$, $-NHC(O)CHF_2$, or $-NHC(O)CF_3$;

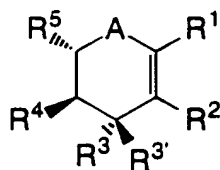
G_1 is guanidino, amino, or guanidino or amino substituted with C_1 - C_5 alkyl;

15

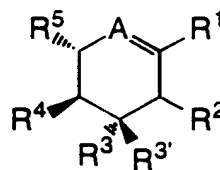
U_1 is C_1 - C_3 alkyl substituted with 1 to 3 C_1 - C_{12} alkoxy groups; and E_1 is $COOH$.

117. A method of treatment or prophylaxis of virus infection in a host comprising administration to the host, by a route other than topically to the respiratory tract, of a therapeutically effective dose of an antivirally active compound of the formula:

20



(x)



(y)

wherein:

in general formula (x), A is oxygen, carbon or sulphur, and in general formula (y), A is nitrogen or carbon;

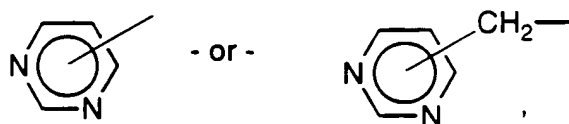
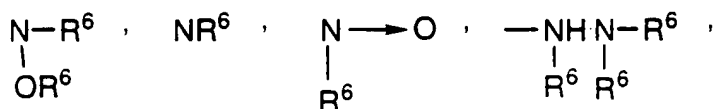
25

R^1 denotes $COOH$, $P(O)(OH)_2$, NO_2 , $SOOH$, SO_3H , tetrazol, CH_2CHO , CHO or $CH(CHO)_2$,

R^2 denotes H, OR^6 , F, Cl, Br, CN, NHR^6 , SR^6 , or CH_2X , wherein X is NHR^6 , halogen or OR^6 and

R^6 is hydrogen; an acyl group having 1 to 4 carbon atoms; a linear or
5 cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted
analogue thereof; an allyl group or an unsubstituted aryl group or an aryl
substituted by a halogen, an OH group, an NO_2 group, an NH_2 group or a
COOH group,

R^3 and $R^{3'}$ are the same or different, and each denotes hydrogen, CN,
10 NHR^6 , N_3 , SR^6 , $=N-OR^6$, OR^6 , guanidino, $-N(H)CN$,



R^4 denotes NHR^6 , SR^6 , OR^6 , $COOR^6$, NO_2 , $C(R^6)_3$, CH_2COOR^6 ,
15 CH_2NO_2 or CH_2NHR^6 , and

R^5 denotes CH_2YR^6 , $CHYR^6CH_2YR^6$ or $CHYR^6CHYR^6CH_2YR^6$, where
Y is O, S, NH or H, and successive Y moieties in an R^5 group are the same or
different,

and pharmaceutically acceptable salts or derivatives thereof,
20 provided that in general formula (x)

(i) when R^3 or $R^{3'}$ is OR^6 or hydrogen, and A is oxygen or sulphur,
then said compound cannot have both

- (a) an R^2 that is hydrogen and
- (b) an R^4 that is NH-acyl, and

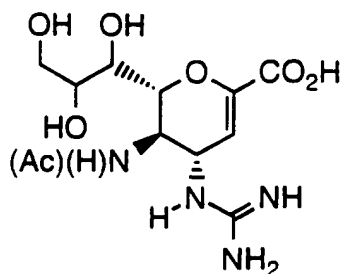
25 (ii) R^6 represents a covalent bond when Y is hydrogen, and that in
general formula (y),

(i) when R^3 or $R^{3'}$ is OR^6 or hydrogen, and A is nitrogen, then said
compound cannot have both

- (a) an R^2 that is hydrogen, and
- (b) an R^4 that is NH-acyl, and

30 (ii) R^6 represents a covalent bond when Y is hydrogen.

118. The method of Claim 117 wherein the compound is of the formula:

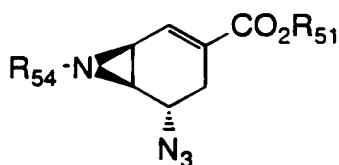


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119. The method of Claim 118 wherein the compound is administered orally.

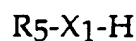
10 120. The method of Claim 119 wherein the host is human or ferret.

121. A method of using a compound of the formula:



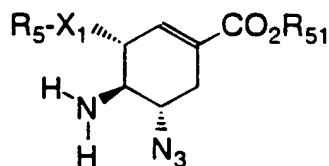
281

15 wherein the method comprises treating compound 281 with a compound of
the formula:



to form a compound of the formula:

20



wherein:

X₁ is -O-, -NR₅-, or -S-;

R₁ is independently H or alkyl of 1 to 12 carbon atoms;

25 R₂ is independently R₃ or R₄ wherein each R₄ is independently substituted with 0 to 3 R₃ groups;

- R₃ is independently F, Cl, Br, I, -CN, N₃, -NO₂, -OR_{6a}, -OR₁, -N(R₁)₂,
 -N(R₁)(R_{6b}), -N(R_{6b})₂, -SR₁, -SR_{6a}, -S(O)R₁, -S(O)₂R₁, -S(O)OR₁, -S(O)OR_{6a},
 -S(O)₂OR₁, -S(O)₂OR_{6a}, -C(O)OR₁, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R₁,
 5 -N(R₁)(C(O)R₁), -N(R_{6b})(C(O)R₁), -C(O)N(R₁)₂, -C(O)N(R_{6b})(R₁), -C(O)N(R_{6b})₂,
 -C(NR₁)(N(R₁)₂), -C(N(R_{6b}))(N(R₁)₂), -C(N(R₁))(N(R₁)(R_{6b})),
 -C(N(R_{6b}))(N(R₁)(R_{6b})), -C(N(R₁))(N(R_{6b})₂), -C(N(R_{6b}))(N(R_{6b})₂),
 -N(R₁)C(N(R₁))(N(R₁)₂), -N(R₁)C(N(R₁))(N(R₁)(R_{6b})),
 -N(R₁)C(N(R_{6b}))(N(R₁)₂), -N(R_{6b})C(N(R₁))(N(R₁)₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)₂),
 10 -N(R_{6b})C(N(R₁))(N(R₁)(R_{6b})), -N(R₁)C(N(R_{6b}))(N(R₁)(R_{6b})),
 -N(R₁)C(N(R₁))(N(R_{6b})₂), -N(R_{6b})C(N(R_{6b}))(N(R₁)(R_{6b})),
 -N(R_{6b})C(N(R₁))(N(R_{6b})₂), -N(R₁)C(N(R_{6b}))(N(R_{6b})₂),
 -N(R_{6b})C(N(R_{6b}))(N(R_{6b})₂), =O, =S, =N(R₁) or =N(R_{6b});

- R₄ is alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or
 15 alkynyl of 2 to 12 carbon atoms;

R₅ is R₄ wherein each R₄ is substituted with 0 to 3 R₃ groups;

R_{6a} is H or an ether- or ester-forming group;

R_{6b} is H, a protecting group for amino or the residue of a carboxyl-
 containing compound;

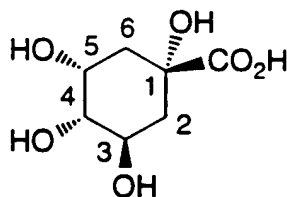
- 20 R_{6c} is H or the residue of an amino-containing compound;

R₅₁ is an acid stable protecting group for a carboxylic acid; and

R₅₄ aziridine activating group.

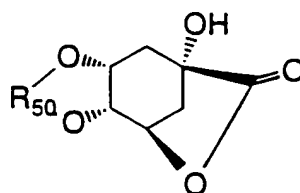
122. A method of using a compound of the formula:

25

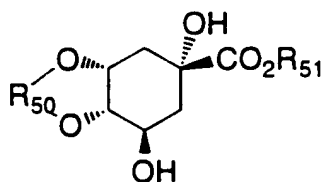


Quinic Acid

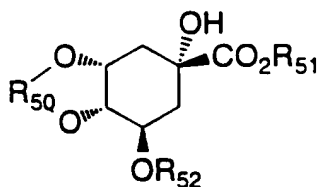
wherein the method comprises treating **Quinic acid** with a geminal
 dialkoxyalkane or geminal dialkoxy cycloalkane and acid to form a compound
 of the formula:

**274**

treating compound 274 with a metal alkoxide and an alkanol to form a compound of the formula:

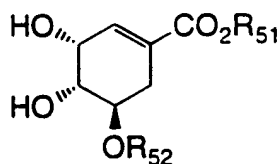
**275**

- 5 treating compound 275 with a sulfonic acid halide and an amine to form a compound of the formula:

**276**

; and

treating compound 276 with a dehydrating agent followed by an acid and an alkanol to form a compound of the formula:

**272**

wherein:

R50 is a 1,2 diol protecting group;

R51 is an acid stable carboxylic acid protecting group; and

R52 is a hydroxy activating group.

123. The composition of Claim 1 where further excluded are compounds wherein G_1 is $-N(R_{21})C(=N(R_{21}))N(R_{21})_2$ and R_{21} is independently H, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkoxy, aryl, aralkyl, aryloxy, aralkyloxy, amino, hydroxy, cyano, nitro, COR₂₂, CO₂R₂₂, SO₂R₂₂ (where R₂₂ is C₁-C₆ alkyl or aralkyl), or CONR₂₃ (where R₂₃ is independently H or C₁-C₆ alkyl or aralkyl).

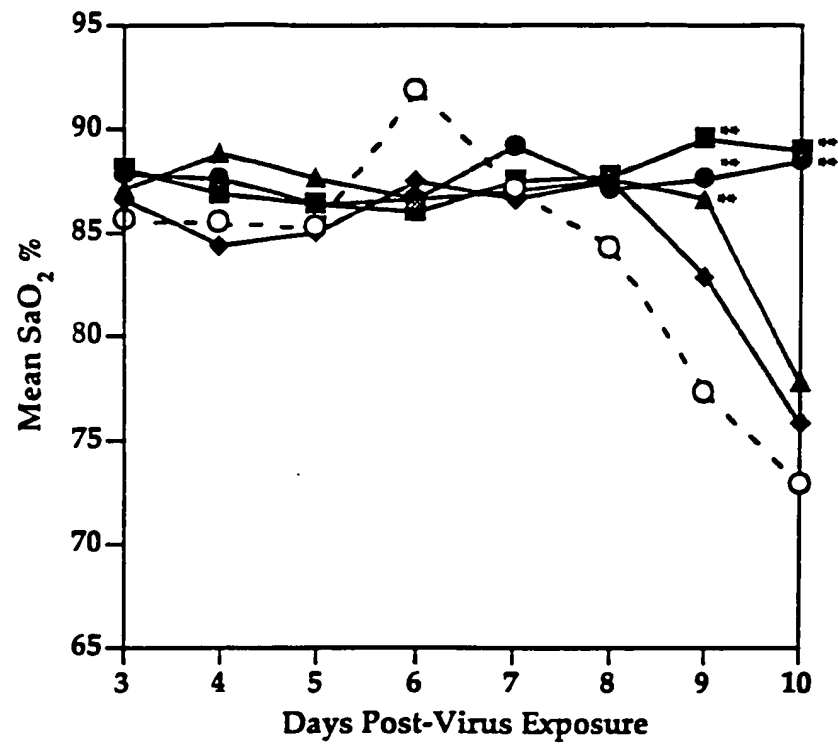


Fig. 1

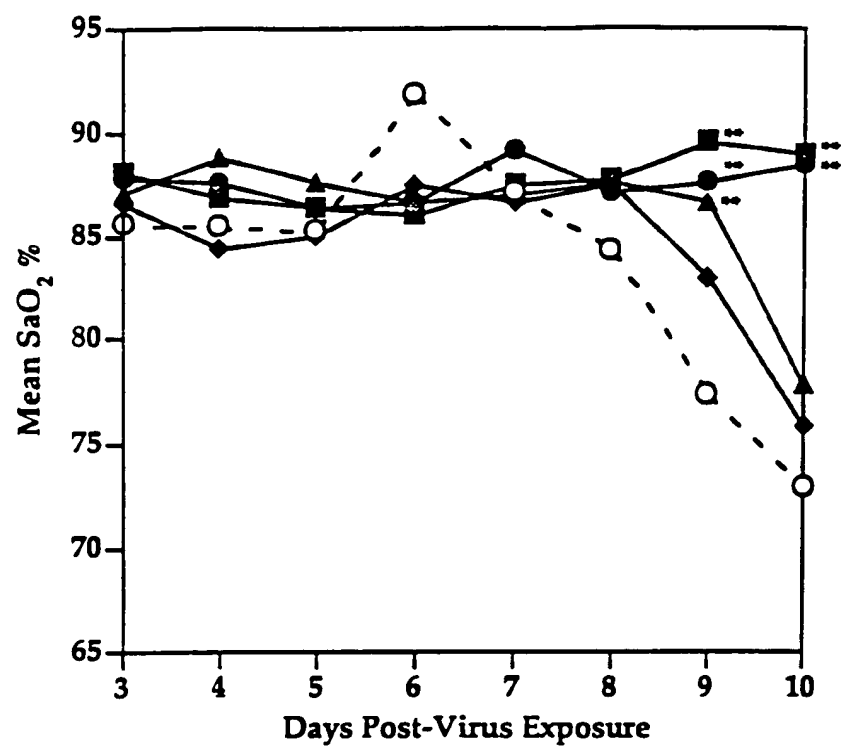


Fig. 2

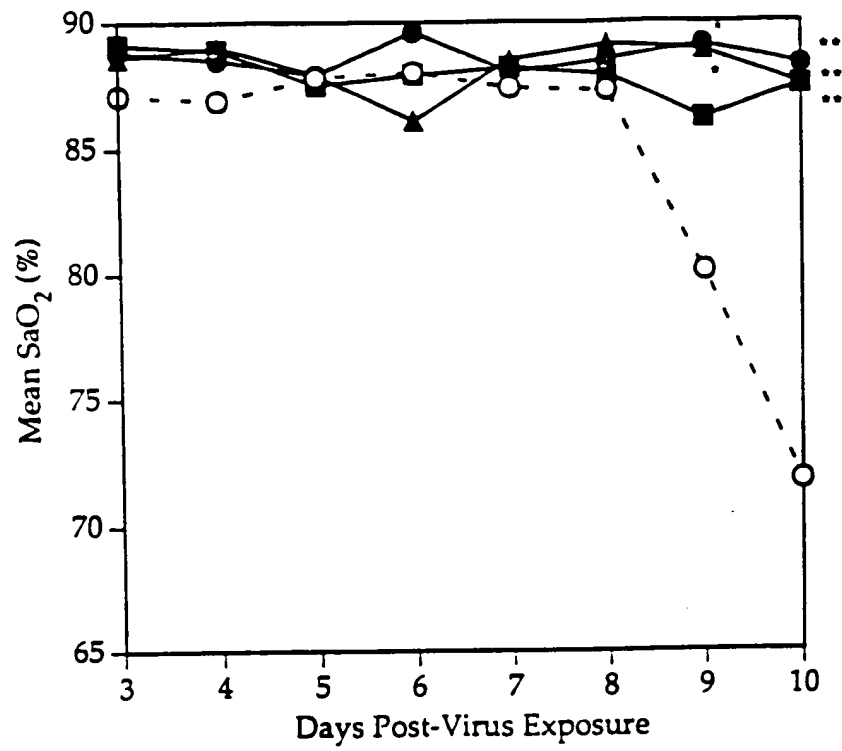


Fig. 3

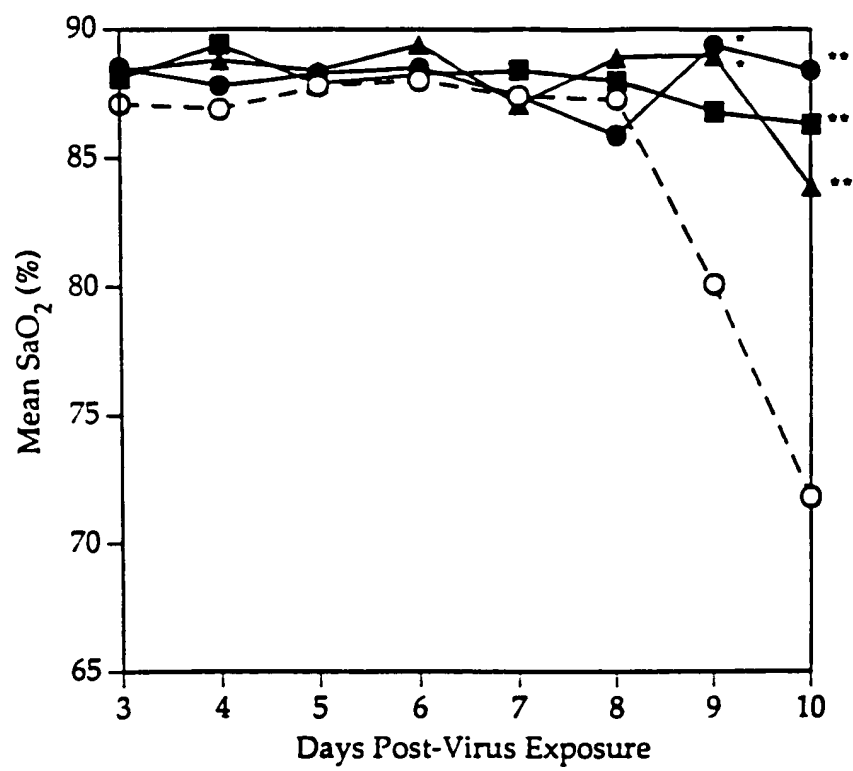


Fig. 4

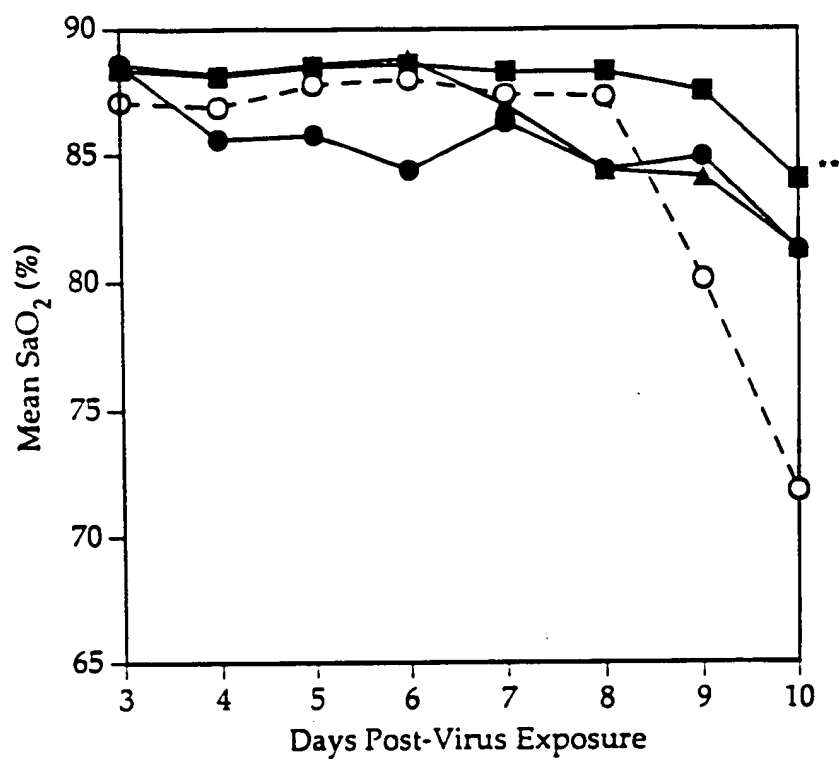


Fig. 5

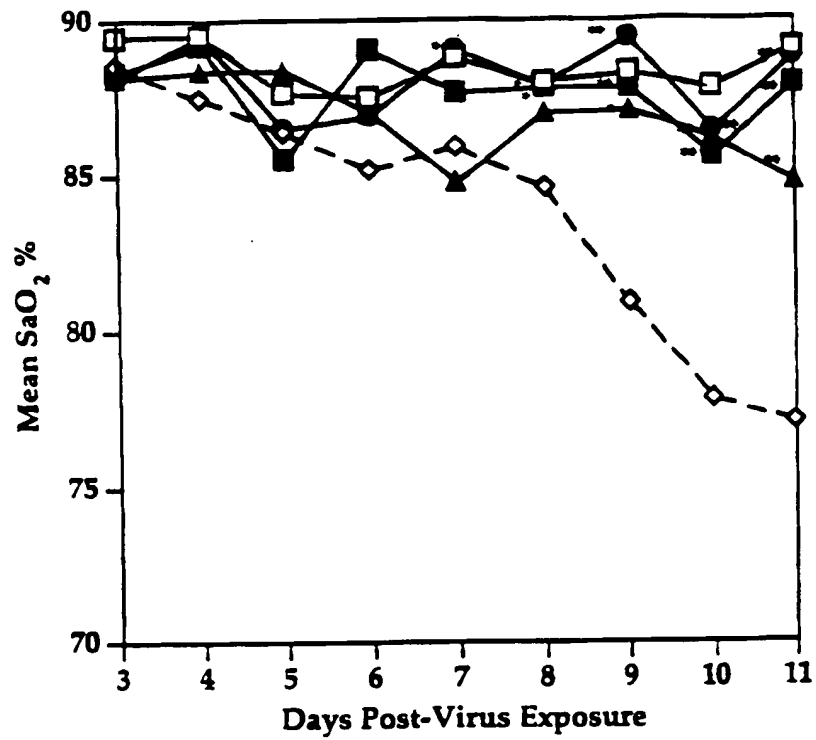


Fig. 6

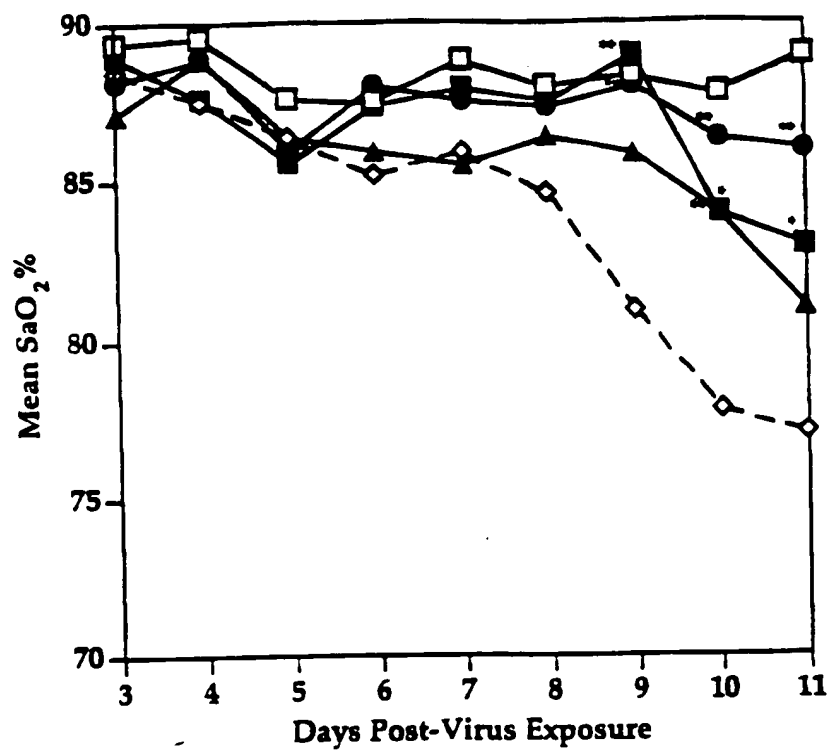


Fig. 7

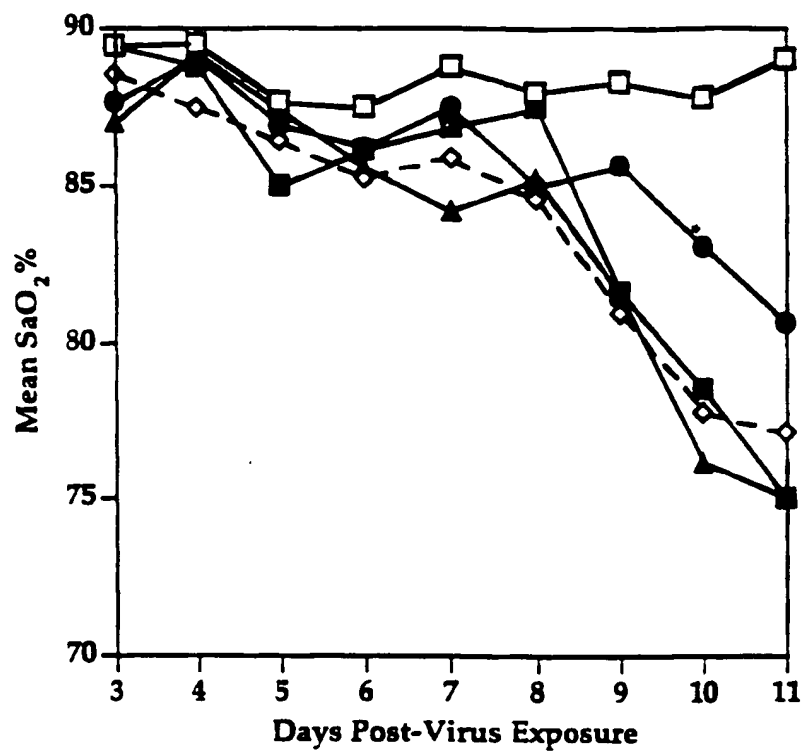


Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/ 02882

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 115-120 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please see attached sheet ./.
Claims 1-117, 121 - 123 have been searched incompletely.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US96/02882

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The generic formulae I and II contain almost no fixed structural moiety. In addition, the large number of values for most of the variables, in conjunction with their cascading meanings and the numerous provisos attached to their definition, renders the scope of the invention for which protection is sought ill-defined and obscure. Consequently, a complete search is precluded for practical and economic reasons.

The search was based upon though not limited to examples given in the description.

For PCT :

(Cf. Arts. 6, 15 and Rule 33 PCT, Guidelines Exam. Part B, Chapt. III, 3.6, 3.7)

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 96/02882

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D309/28 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 06691 (BIOTA SCIENT MANAGEMENT) 30 April 1992 cited in the application see claims 1,12,22 see table 1	1-123
X	--- WO,A,91 16320 (BIOTA SCIENT MANAGEMENT) 31 October 1991 cited in the application see page 5 see claims 1-19 see table 1 see examples 1-19	1-123
X	--- EP,A,0 539 204 (BIOTA SCIENT MANAGEMENT) 28 April 1993 cited in the application see the whole document ---	1-123
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

9 July 1996

Date of mailing of the international search report

18.07.96

Name and mailing address of the ISA

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Authorized officer

Kissler, B

INTERNATIONAL SEARCH REPORT

Inter- national Application No
PCT/US 96/02882

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>NATURE (LONDON) (1993), 363(6428), 418-23 CODEN: NATUAS;ISSN: 0028-0836, 1993, XP000574955 VON ITZSTEIN, MARK ET AL: "Rational design of potent sialidase-based inhibitors of influenza virus replication" see table 2 -----</p>	1-123

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/02882

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9206691	30-04-92	NONE	
WO-A-9116320	31-10-91	AP-A- 249 AU-B- 7533891 AU-B- 654815 AU-B- 7759091 CN-A- 1057260 EP-A- 0526543 HU-A- 61989 IL-A- 97936 OA-A- 9679 PL-B- 167192 PL-B- 166918 PL-B- 167630 US-A- 5360817	17-03-93 12-12-91 24-11-94 11-11-91 25-12-91 10-02-93 29-03-93 08-12-95 15-05-93 31-08-95 31-07-95 31-10-95 01-11-94
EP-A-0539204	28-04-93	AU-B- 2724292	29-04-93